ASSESSMENT OF EXECUTIVE FUNCTION IN TYPE 2 DIABETES MELLITUS – A CASE CONTROL STUDY

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
In partial fulfillment of the regulations
for the award of the degree of

M.D. BRANCH - XVIII
M D. Psychiatry

INSTITUTE OF MENTAL HEALTH
MADRAS MEDICAL COLLEGE

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, INDIA

APRIL 2015

CERTIFICATE

This is to certify that the dissertation titled, **"ASSESSMENT OF EXECUTIVE FUNCTION IN TYPE 2 DIABETES MELLITUS – A CASE CONTROL STUDY"** is the bonafide work of **Dr. MYTHILI. V** in part fulfillment of the requirements for M.D. Branch – XVIII (Psychiatry) examination of The Tamilnadu Dr. M. G. R. Medical University, to be held in APRIL 2015. The period of study was from July 2014 – September 2014.

The Director,

Institute of Mental Health
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CERTIFICATE OF GUIDE

This is to certify that the dissertation titled, **"ASSESSMENT OF EXECUTIVE FUNCTION IN TYPE 2 DIABETES MELLITUS – A CASE CONTROL STUDY"** is the original work of **Dr. MYTHILI. V**, done under my guidance submitted in partial fulfilment of the requirements for M.D. Branch – XVIII [Psychiatry] examination of The Tamilnadu Dr. M. G. R. Medical University, to be held in April 2015.

Signature

DECLARATION

I, **Dr. MYTHILI. V** solemnly declare that the dissertation titled, **"ASSESSMENT OF EXECUTIVE FUNCTION IN TYPE 2 DIABETES MELLITUS – A CASE CONTROL STUDY"** is a bonafide work done by me at the Rajiv Gandhi Government General Hospital, Chennai, during the period from July 2014 – September 2014under the guidance and supervision of Dr. R. JEYAPRAKASH M.D, D.P.M, Professor, Institute of Mental Health Madras Medical College.

The dissertation is submitted to The Tamilnadu Dr. M. G. R. Medical University towards part fulfillment for M.D. Branch XVIII (Psychiatry) examination.

Place: Chennai **Dr. MYTHILI . V**

Date: 25/09/2014

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Dr. MYTHILI . V

Date: 25/09/2014

Place: Chennai

INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
Dr. V. Mythili,
Final Year Postgraduate in MD Psychiatry,
Institute of Mental Health,
Chennai – 600003.

Dear Dr. V. Mythili,

The Institutional Ethics Committee has considered your request and approved your study titled **"Executive functioning in Type II Diabetes Mellitus – A case control study"** No. 51072014.

The following members of Ethics Committee were present in the meeting held on 01.07.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
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5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE

Member Secretary, Ethics Committee

Diabetes Mellitus and Executive Function

INRODUCTION

38 Diabetes mellitus type 2 is a metabolic disorder characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin[1,2]. Type 2 Diabetes Mellitus [T2DM] is being described as a modern day epidemic, emerging rapidly in developing countries[1]. T2DM 24 is a major public health problem all over the world[3]. The soci0-economic cost of 24 Type 2

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Diabetes Mellitus and Executive Function

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Diabetes mellitus type 2 is a metabolic disorder characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin[1,2]. Type 2 Diabetes Mellitus [T2DM] is being described as a modern day epidemic, emerging rapidly in developing countries[1]. T2DM is a major public health problem all over the world[2]. The socio-economic cost of Type 2 diabetes mellitus is exorbitant, mainly due to number of associated problems that accompany diabetes mellitus, like micro and macro vascular diseases and their increased susceptibility for cognitive impairment[1,2].

Executive function is a primary domain of cognition that involves a broad set of cognitive abilities like attention, working memory, organization, and persistence that are necessary for orchestrating

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ASSESSMENT OF EXECUTIVE FUNCTION IN TYPE 2 DIABETES MELLITUS – A CASE CONTROL STUDY

Abstract

Introduction:

Type2 Diabetes Mellitus is associated with inherent micro-vascular disease affecting frontal sub-cortical function. Executive Dysfunctions are implicated in decreased self-care capacity, poor adherence to diabetic medication, decreased levels of autonomy and a decrease in ability to make essential decision, for instrumental activities of daily living, as well as resistance to proper medical care.Isolated executive impairment falls within the category of “mild cognitive impairment. Studies have shown that patients with Type 2 DM performs significantly poorer in Executive Function compared to normal subjects .Hence this study was proposed to assess the executive Function of Type 2 DM patients.

Aim &Objective:

To assess executive functioning in type 2 diabetic patients compared to normal subjects.

Methods:

The study is a cross sectional observational case control study,conducted at the Rajiv Gandhi Government General Hospital(RGGGH), Chennai. 50 patients attending outpatient department of Diabetology, fulfilling the inclusion criteria were randomly chosen and included in the study. Fifty consenting age, sex, education matched normal people who were relatives of patients attending RGGGH OPD were taken as controls. Both the study population and controls were administered the semi structured proforma. Then GHQ and HAM D was administered to screen for psychiatric symptoms. Those who scored positively were excluded from the study. MMSE was administered as a screening tool for cognition. All diabetes mellitus patients were tested for their blood glucose level before administering

the evaluation tests. This was done to avoid hypoglycemia /severe hyperglycemiaaffecting the executive function assessment. The following parameters were assessed - Proforma for socio demographic data of study cases and control group, Proforma for Diabetes Status, Mini Mental State Examination (MMSE), Test for Executive Function namely Digit Span Test,Verbal fluency , Trail making test, Stroop Test, Wisconsin Card Sorting Test. The data collected were analysed using Chi square test and Wilcoxon – Mann-Whitney U test.

Result:

Comparison of socio-demographic data of cases and controls shows no significant difference. The mean age of onset of diabetesmellitus is 41.40 years and the duration of illness was < 5 years. There was no major macro / micro vascular complication. Comparison of neuropsychological scores between cases(study group) and controls with Digit Span Test,Verbal fluency , Trail making test, Stroop Test, Wisconsin Card Sorting Test was done.In Digit Span Test,Verbal fluency, Stroop Test& Wisconsin Card Sorting Test did not show statistical significance. Trail making test showed statistical significance.

Conclusion:

Executive functioning in diabetics was comparable to that of control group. Though Trail making test, showed a statistical difference between diabetics and non-diabetic, it was still within the normative Range for the particular age group. Validation of this conclusion requires a larger group and prospective longitudinal study.

Keywords :

Executive function, Diabetes Mellitus, Stroop Test, Wisconsin Card Sorting Test

INRODUCTION

Diabetes mellitus type 2 is a metabolic disorder characterized by hyperglycemia in the context of insulin resistance and relative lack of insulin[1, 2].Type 2 Diabetes Mellitus is being described as a modern day epidemic, emerging rapidly in developing countries[1]. Type2 diabetes mellitus is a major public health problem all over the world[3]. The socio-economic cost of Type 2 diabetes mellitus is exorbitant, mainly due to number of associated problems that accompany diabetes mellitus, like micro and macro vascular diseases and their increased susceptibility for cognitive impairment[1,2].

Executive function is a primary domain of cognition that involves a broad set of cognitive abilities like attention, working memory, organization, and persistence that are necessary for orchestrating complex, goal-directed activities[3]. Executive function appears to be orchestrated and mediated by frontal cortex along with its networks in cerebrum and sub-cortical regions of brain[4].Though it is known that diabetes is related to some domains of cognition such as processing speed and memory, greater

attention is now being directed to the association and causal link between diabetes and executive functioning domain of cognition[1,5]. Recent studies and evolving data categorically suggest that executive dysfunction is causatively associated with poor glycemic control[2,5] i.e. it is one of the major risk factor. The effect of Type2 diabetes mellitus on executive function is associated with inherent micro-vascular disease affecting frontal sub-cortical function[1].

Executive function is a major domain of cognition that plays a pivotal role in allowing the execution of daily management tasks including exercise, blood glucose monitoring and drug intake, which are essential for glycemic control[1]. Executive Dysfunctions are implicated in decreased self care capacity, poor adherence to diabetic medication, decreased levels of autonomy and a decrease in ability to make essential decision, for instrumental activities of daily living, as well as resistance to proper medical care[1,5]. Individuals with Type2 diabetes mellitus perform significantly poorer in executive functional measures compared to normal adults.

The purpose of this study is to assess executive function in patients with type 2 Diabetes mellitus in comparison to normal subjects.

REVIEW OF LITERATURE

EXECUTIVE FUNCTION

DEFINITION:

In this modern world with a frequently changing environment, we are constantly facing altered circumstances that require, continuous generation and credible monitoring of appropriate strategies, for which newer ways of action have to be formulated and conducted[3].

The specific abilities that are called upon to respond accurately to newer situations are referred to as Executive Functions. This domain of cognitive functions is used for usually managing the conditions in which routine activation of behavior would not be sufficient for optimal performance, and hence in those conditions a top-down control is required to adjust or modify behavior[4].

The Diagnostic and Statistical Manuel of Mental Disorders, fourth edition, defines executive function as one's ability to plan, initiate, sequence, monitor and inhibit complex goal directed behavior[3].

Executive function is a set of cognitive process that allows one to behave independent of the environment, instead of having behaviors mediated by the environment[4].

Psychodynamic Diagnostic Manual – defines executive function as cognitive abilities necessary for complex goal directed behavior and adaptation to a range of environmental changes and demands. Functions include the ability to plan and anticipate outcomes (cognitive flexibility), the ability to direct attentional resources to meet the demands of non-routine events.

American psychiatric association describes executive function as a set of cognitive abilities that control and regulate other abilities and behaviors. They include ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel task and situation[3].

Two central themes of executive control framework are[4]

Self regulatory skills

Perception

Modulation

Sustained attention

Flexibility

Working memory

Response inhibition

Emotional regulation

Goal oriented skills

Planning

Organization

Time management

Self monitoring

Executive functions comprise a set of skills which are responsible for orchestrating goal oriented activities like finances, medications, transportation, shopping, cooking, housework, and using multimedia and communication devices[4,5].

These activities constitute the Instrumental Activities of Daily Living[4].These activities are made possible through successful planning, initiation, sequencing with ongoing monitoring and assessment for possible adjustments of goals or actions. Similar to other cognitive

functions, such as language and memory, these are acquired skills. Intact executive functions are thus vital to human autonomy[4].

Anatomically, the pre-frontal cortex and its basal ganglia connections are responsible for executive functioning[2]. It is however difficult to exactly localize or pinpoint specific executive functions to specific areas within the frontal cortex. The frontal cortex is connected to the caudate, putamen, pallidum and thalamus via circuits[2]. These connections are intrinsically and dynamically balanced direct and indirect circuits. The importance of these connections is manifested by the fact that executive impairment may occur without direct frontal damage, that is by disruption of these dynamic circuits[2,6].

Isolated executive impairment falls within the category of “mild cognitive impairment”. Mild cognitive impairment is heterogeneous group of disorders[6] which does not meet the criteria for dementia. Executive impairment was added to the definition of dementia by the American Psychiatric Association in 1994[7].

The introduction of diagnosis – Mild Neurocognitive disorder is crucial change in diagnostic criteria for neurocognitive disorder in DSM – V Individuals often seek medical and psychiatric evaluation for neurocognitive problems that do not meet the criteria for major neurocognitive disorder.

DSM – V also includes complex attention, Executive function, peripheral motor problems, and social cognition among neurocognitive domains that can be impaired by a neurocognitive disorder.

These individuals frequently fall below the normal range of function on neuro-psychological testing, but their signs and symptoms are not severe enough to be classified as major neurocognitive disorder or dementia.

Although they may be living independently, they struggle with activities of daily living and express this difficulty. Mild Neurocognitive Impairment is often found to be a transitional stage between aging and dementia. Although Mild Neurocognitive Impairment can present with a variety of symptoms, when memory loss is the predominant symptom it is termed as Amnesic Mild

Neurocognitive Impairment, and is frequently seen as Prodromal stage of Alzheimer's dementia.

When Individuals have impairment in domains other than memory, it is classified as Non Amnesic, single or multiple domain Mild Neurocognitive Impairment and the individuals are more likely to convert to other dementia.

IMPACT OF EXECUTIVE IMPAIRMENT ON THE INDIVIDUAL:

Executive impairment has been shown to be strongly associated to a number of chronic medical diseases[1, 2,7]. More commonly associated conditions include schizophrenia, major depressive disorders, chronic obstructive airway disease, obstructive sleep apnea syndrome, congestive heart failure, infection with Human Immunodeficiency Virus, chronic renal failure, lung cancers, hypertension, subcortical ischemic vascular disease, pituitary tumors and type 2 diabetes mellitus[1,2,7].

During the normal aging process deterioration of executive function correlates with longitudinal decline in functional status, and thus may be considered a predictor

of functional status. Freedom House Study[7] showed that in patients with chronic diseases executive dysfunction may be viewed as a predictor of severity and disability.

Tests of executive function correlate strongly with instrumental activities of daily living rather than physical activities of daily living[8]. Executive functioning is able to discriminate between independent patients, patients requiring moderate level supervision and those requiring full supervision[1], there by a guiding in level of supervision required.

Self-management is regarded as a set of skilled behaviors used to manage one's illness. This places greater responsibility on the individual for disease management. Executive impairment impacts negatively on a patients' ability to self-manage their disease. It hinders their ability to adhere to treatment regimens and implement necessary lifestyle changes. These patients have also been found to be much more resistant towards effective care and suffer from impaired medical-decision-making capacity[8,9].

Patients with executive impairment are less likely to self-report their impairment and / or difficulty than those

with memory impairment, and more frequently may report it as memory loss rather than executive dysfunction. However impaired executive function may have a more profound effect on ones autonomy than impaired memory[1, 10, 11].

TYPE 2 DIABETES MELLITUS AND COGNITION:

DEFINITION:

According to WHO, the term diabetes mellitus describes a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia, with disturbance of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action, or both[13]. Type 2 diabetes mellitus is a non-autoimmune, complex, heterogeneous and polygenic metabolic disease condition in which the body fails to produce enough insulin, characterized by abnormal glucose homeostasis[14].

Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision and weight loss. In its severe forms, ketoacidosis or a non-

ketotic hyperosmolar state may develop and lead to stupor, coma and in absence of effective treatment, death.

Type 2 diabetes mellitus is associated with a relative impairment in insulin secretion coupled with varying degrees of peripheral resistance to the action of insulin. Type 2 diabetes may also be considered a syndrome with multiple associated co-morbidities and complications[15]. The associated insulin resistant state of type2 diabetes is fundamental to the pathogenesis of the metabolic syndrome[10].

The long term effects of diabetes mellitus include retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcer, amputation, Charcot joints, and features of autonomic dysfunction, including sexual dysfunction. People with diabetes mellitus are at increased of cardiovascular, peripheral vascular and cerebrovascular disease[16].

Diabetes is the potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.[17,18,19] It is estimated that by 2030

diabetes mellitus may afflict up to 79.4 million people in India[19].

GLOBAL BURDEN OF TYPE 2 DIABETES MELLITUS:

International Diabetes federation has reported that the prevalence of Type 2 diabetes mellitus have reached epidemic proportions all over the world. Estimated number of Type 2 Diabetes mellitus in the year 2010 was around 2,850,000 in 7 regions of International Diabetes Foundation. The International Diabetes Foundation had estimated that around 3,900,000 deaths were caused by diabetes in 2010 which is about 6.8 percent of the total number of death globally[20]. It is estimated that by the year 2030, more than 75.5 percent of the total global population with diabetes will be the inhabitants of the developing world countries and the countries expected to be with largest population of Type 2 diabetes mellitus in the world are 1.India(79.4%), 2.China(42.3%),3.United States of America(30.3%)[21].

In developing countries, the major proportion of adults patients with Type 2 diabetes mellitus are between 45 years and 64 years of age, while in the developed

countries, most of the Type 2 Diabetes Mellitus patients are 65 years of age and above. The International Diabetes Federation estimates that 23,000,000 years of productive life span are lost to disability as well as reduced quality of life, as a direct impact of the complication associated with Type2 diabetes mellitus[20].

Diabetes is a complex disease that requires intensive self-care. The executive function seems to be essential to carry out the day to day management tasks including exercise, blood glucose monitoring and drug intake, which are pre-requisite for adequate glycemic control. Impairments in executive functional ability leads to reduction in self-care capacity, as well as poor adherence to the essential diabetic medication, low independence. Executive dysfunction is also responsible for their inability to make appropriate decisions, low autonomy in instrumental activities of daily living, as well as reluctance to care. Type 2 diabetes mellitus patients perform significantly worse on executive functional measures relative to normal comparison adult population[10.11].

DIAGNOSIS OF TYPE 2 DIABETES MELLITUS:

AMERICAN DIABETES ASSOCIATION CRITERIA DIAGNOSIS OF DIABETES MELLITUS[22]:

The American Diabetes Association (Diabetes Care 28:S4-S36, 2005) stated that diabetes can be provisionally diagnosed using any 1 of the following 3 criteria.

1. Fasting plasma glucose >126 mg/dl (after nil intake for at least eight hours)

2. Casual plasma glucose >200 mg/dl (taken randomly at any time of day) and associated diabetes mellitus symptoms:

   Polyphagia, polydipsia, polyuria and unexplained weight loss of more than 10%

3. Oral glucose tolerance test (GTT) (seventy five grams dose) >200 mg/dl for the 2 hour blood sample. GTT is unnecessary if patient's FPG is >126 mg/dl.

The American Diabetes Association prefers the fasting plasma glucose compared to GTT for diagnosing Diabetes mellitus.

IMPACT OF TYPE 2 DIABETES ON COGNITION:

Diabetes mellitus is recognized to be associated with cognitive dysfunction and cognitive abnormalities[23,24]. Neuropsychological tests have demonstrated deficits in various aspects of cognition in both young and elderly diabetics[23]. Deficits affect global cognition, psychomotor efficiency, episodic memory, semantic memory and working memory[24,25]. Cognitive decrements may occur at two separate intervals of cognitive vulnerability:

1. During brain development, ages 5-7 years, typically this would refer to type 1 diabetes.

2. Later on they may develop within the neurodegenerative phase, generally from age 65 years onwards. This would be accounted for in the majority by type 2 diabetes. Outside of these two periods it would need to occur in the face of both micro-vascular and macro-vascular target organ damage[26].

Diabetes mellitus is a risk factor for neurological conditions of ageing; these include all forms of dementia and cognitive decline[27]. The impact of diabetes mellitus on

cognition has been of interest for at least past 8 decades. It was first explored by Miles and Root who demonstrated impaired memory, poor mental arithmetic, and slowed psychomotor efficiency in type 1 diabetics exclusively. They hypothesized that the main underlying mechanism might be recurrent hypoglycemic episodes. However this was disputed when later cognitive impairment was also significantly associated with type 2 diabetics, in whom chronic hyperglycemia was thought to be responsible[12].

STUDIES SHOWING SIGNIFICANT CORRELATIONS:

In a cross-sectional study of 28 patients with diabetes and 28 non-diabetic controls, Dey et al (1997) found some association between cognitive impairment in people with diabetes aged 55 years and younger. When comparing people with Type 2 diabetes and people without the condition, Grimley Evans and Areosa Sastre (2003) found an up to twofold increase in the risk of cognitive impairment or dementia in people with diabetes[28].

Kumari and Marmot (2005), in a prospective cohort study of 4020 men and 1627 women (mean age 56 years) comparing cognitive performance in three groups – those

with diabetes, impaired glucose tolerance, and normoglycemia, concluded that type 2 diabetes was associated with impairment some aspects of cognition, particularly verbal and mathematical reasoning, in middle-aged men and women[32].

Kuo et al in 2005[34] evaluated 2,802 community dwelling aged adults (of which 358 had diabetes) for cognition and physical function, along with their status of activity of daily living. He reported that there is a stastistically significant increased rate of decline in performance on an executive function of attention in those with diabetes mellitus than in people without diabetes mellitus. This decline in executive measure of attention had a compounded match of a increased rate of decrease in performance on the physical function part of the Medical Outcomes Study Health Survey (SF-36) questionnaire. A similar result was found by measures of Activities of Daily Living functioning assessing works/jobs - meal preparation, homework, finance and health management, telecommunication use, shopping, and travelling.

Arvanitakis et al (2006), in the Rush Memory and Aging Project, a longitudinal clinical pathological study that recruited 882 participants aged 80.5 (± 6.9 years) from retirement facilities in Chicago, assessed episodic, semantic, working memory, perceptual speed, visuospatial ability and global cognition and concluded that diabetes is associated with lower levels of semantic memory and perceptual speed. Associations were reduced when controlling for several vascular variables and were substantially stronger in current smokers[29,30].

Many researchers have reported impaired performance on a number of executive function requiring tasks in older adults with type 2 Diabetes Mellitus. Many longitudinal investigations of type 2 Diabetes Mellitus and cognition had shown a significantly increased risk of executive function decline[52]. Qiu WQ et al in2006[35] assessed the cognitive function of 291 people older than sixty years of age and who were home bound. He found that people with type 2 diabetes mellitus (115), demonstrated significantly more deficits inn executive function measures - updating or working memory(7%), reasoning(17%), and in

shifting(21%). These findings were consistent with other longitudinal datas describing a small and significant deficits over baseline of approximately –10 percentage—in measures of attention (55) and shifting (682) in older adults who had type 2 Diabetes mellitus. A longitudinal follow-up showed that these people with diabetes mellitus had two fold increase in the risk of decline on both these measures of executive function, over four year and six year periods.

One of the strongest evidence for type 2 diabetes mellitus causing executive dysfunction arises from an analysis by Yeung etal(2009)[36] .He administered multidimensional executive function assessment battery to 465 older adults, of which 41 had type 2 Diabetes Mellitus. Those without diabetes mellitus scored up-to 12% and 14% higher than those with diabetes on executive function measures of inhibition and shifting. This type of detrimental effect of diabetes mellitus on executive function continued to remain significant even after the study sample was divided into two groups –

1. young-old (53–70 yrs)

2. old-old (71–90 years),

There by suggesting that the impairments were more likely to be mediated by diabetes mellitus status of the patient, rather than by age of the patient

Alvarenga et al in 2010[37] compared the functional mobility, the risk of falls and the executive function among elderly with and without type 2 diabetes. They concluded that diabetics presented worse performance in the functional mobility and in the verbal fluency test than non-diabetics elderly that suggests a greater risk of falls for the elderly with diabetes.

Rucker JR, Jernigan SDamong etal in 2011[38] did the one of the first pilot study to examine executive abilities in adults with diabetes across a range of EF domains. They found diabetic individuals demonstrated intact performance on many measures, they appear to exhibit deficits in executive tasks involving verbal fluency and organization, perceptual organization and planning, and time sharing.

Similarly, Nooyens et al (2010) measured cognitive functioning in diabetic and non-diabetic adults aged 43-70, twice in a 5 year interval and found that those patients with type 2 diabetes mellitus showed a greater decrease in cognitive functional measures than those individuals without diabetes mellitus[33].

It is not easy to measure cognitive impairment in diabetes directly given diabetes' association with other risk factors such as hypertension and dyslipidemia, and other comorbidities including cardiovascular disease, all of which have been shown to interact with cognition (Perlmuter et al. 1988[51]; Larkin 2001[58] Messier et al. 2004[49,50] Van Den Berg et al. 2010[60]).

Solanki etal in 2010 studied the association of diabetes mellitus with cognitive functioning and depressive features in 50 diabetic and 30 control subjects, and concluded that though genesis of cognitive deficits in diabetic patients is complex, it may be associated with chronically poorly controlled diabetes[44].

Mukherjee et al in 2012[45] determined the relationship between diabetes and cognitive impairment is respect of

the age of onset and duration of diabetes, other complication of diabetes mellitus and effect of short term glycemic control on cognitive impairment. 50 diabetic patients were assessed by ―Kolkata Cognitive Screening Battery. They found that cognitive decline was associated with diabetes but not directly related to the duration and age of onset of diabetes and control of diabetes lead to improvement of cognitive function.

Subha et al in 2012 evaluated the cognitive functional status of type 2 diabetes mellitus patients and non-diabetes controls using the Mini Mental Status Examination and the Modified Mini Mental Status Examination . They concluded that type 2 diabetes mellitus is associated with lesser levels of performance of cognitive function[46].

H. Nicolae, C. Panea etal in 2012[59] assessed cognitive function of a group of 23 type 2 diabetes mellitus patients who were between 40 and 68 years of age. The global cognitive score for diabetic patients was significantly low – 60.3/100 pts when compared to control group - 69.08/100 pts (p 0.048). The cognitive field most affected in these patients was the executive function 7.30/20 points in

diabetic patients compared to that of the control group – 11.04/20 points($p = 0.008$). Their inference was that type 2 Diabetes Mellitus patients had a lower cognitive score, even at middle-age, when compared with patients without this type of diabetes mellitus. The concluded that domain that is more affected than other domains of cognition is the executive function.

Marzieh Nazaribadie et al in 2014[47] assessed the executive functions and information processing in type 2 diabetes mellitus patients in comparison to pre-diabetes patients and normal subjects. Executive functions were assessed by Wisconsin Card Sorting Test in 28 diabetic s, 28 prediabetics and 30 controls. The pairwise comparisons of executive functions among three groups suggest a significant difference between diabetic and normal groups in Wisconsin Card Sorting Test (perseveration) $p = 0.018$, and significant difference between diabetic and pre-diabetic patient in Wisconsin Card Sorting Test (perseveration) $p = 0.019$. They concluded that there were significant differences in executive function and

information processing in patients with in type 2 diabetes mellitus and normal individuals.

STUDIES SHOWING INSIGNIFICANT CORRELATIONS:

Deborah Amanda Goh et al in 2014[48]did a pilot study, to evaluate the clinical association between level cognitive impairment and the biochemical perturbations that occur in Type 2Diabetes Mellitus, and the impact of HMG Co A Reductase inhibitors (statins) treatment on cognitive function in Type 2 diabetes mellitus patients. They concluded that overall cognitive function was similar among diabetes mellitus patients and non-diabetes controls. Among diabetes mellitus patient with HMG-CoA reductase inhibitors users, High Density Lipoproteins, Low Density Lipoproteins and total cholesterol had a negative correlation with executive function, whereas peripheral levels of insulin and insulin resistance had a negative correlation with attention. Diabetes mellitus patient with HMG-CoA reductase inhibitors users were expected to have a decreased level performance in the areas of attention and executive function. Elevated levels of the

biomarkers are also expected to contribute to poorer cognitive performance.

Depression, which has been shown to be more common in people with diabetes than their healthy counterparts (Amato et al. 1996[39]; Moussavi et al. 200741; Anderson et al. 2012[40];), can exacerbate or be mistaken for cognitive impairment or even the early stages of dementia (Visser et al. 2000[42]; Swainson et al. 2001[43]). Many studies have looked at cognition, but often have taken global measures of cognitive function. This approach may overlook types of cognitive impairment that affect specific areas of function but not others. Also, studies that have looked at specific areas of cognition have been extremely varied in their study designs and participants selected.

The effect of type 2 diabetes mellitus on executive function had not been demonstrated consistently and uniformly across all studies. Many Authors have shown a negative correlation between diabetes mellitus and executive dysfunction.

Lynnp. Lowe et al in 1994[54] explored the relationship between type II diabetes and cognitive function in 80

diabetic and 81 non-diabetic older Native Americans and assessed the effects of other selected risk factors for cognitive dysfunction on this relationship. They found little evidence that type II diabetes in this population of Native Americans was associated with decrement in cognitive function. Saczynski JS etal in 2008[55] evaluated 1,917 old aged people (218 had type 2 Diabetes mellitus) for executive dysfunction and found that there was no significant executive dysfunction on a composite evaluation of updating and inhibition tasks. Ruis et al in 2009[56] observed that there is no impairments on a set of un-specified executive tasks for a sample of 183 old aged adults with recently diagnosed type 2 Diabetes Mellitus. The results were in agreement with prior literature reviews, which describe an inconsistent relationships of affects of type 2 Diabetes Mellitus on executive function.

Paul et al in 2009[57] evaluated elderly diabetics with or without peripheral neuropathy, by asking them to perform a serial mental subtraction task, and carrying of a tray with water-filled cups during walking. It was found to significantly slow the gait speed in 15 of them with

diabetes mellitus and no clinical signs of peripheral neuropathy by approximately 27%. These tasks also decreased step length in these diabetes mellitus with no peripheral neuropathy by up to 20% and increased their double-support time by approximately 17%. These changes did not show any statistically significant difference when compared to the ones elicited in with diabetic mellitus patients with peripheral neuropathy. This seems to re-emphasize a gross and vital limitation in the executive function ability that is needed to divide the attention between the various tasks, which is a central limitation, rather than a limitation occurring due to somato-sensory neural pathway affection in the form of diabetic neuropathy, which is a peripheral limitation.

POSSIBLE MECHANISMS OF IMPAIRED COGNITION:

Cognitive dysfunction in diabetes mellitus range from subclinical to subtle to severe deficit like dementia[61]. Cognitive function is affected in diabetes mellitus by

Hypoglycemia

Hyperglycemia

Hyperinsulinemia

Executive Dysfunction and Hypoglycemia:

The brain being an high energy consuming organ, it utilizes upto 25% of total body glucose for adequate functioning[62]. The normal blood glucose level is a range between 3.9 to 7.1 mM (1 mM ~18 mg/dl). Blood glucose level below which brain function deteriorates is 3 mmol/l(54 mg%). In Diabetes Mellitus patients, not only severe hypoglycemia (<2 mmol~ 36mg%) but also recurrent mild (3.2 - 3.6 mmol~ 58 - 64mg%) or moderate (2.3 -3.2 mmol~42 -58mg%) hypoglycemia have deleterious affects on brain[62-65]. Latter two (recurrent mild and moderate) are significantly more common than severe hypoglycemia[65]. Hypoglycemia occurs more commonly with intensive insulin therapy[65].

Acute hypoglycemia affects attention, mental flexibility and associative learning[66,67]. Recurrent mild and moderate hypoglycemia causes greater level of intellectual

decline especially with performance IQ, impaired mental abilities and short term memory deficits[66]. Many experimental as well as clinical studies have shown that severe hypoglycemia for a duration of least ten minutes result in activation of microglial cells. The oxidative stress that occurs results in release of many neuro-toxic substances, like superoxide(SO3), nitric oxide(NO), and metallo-proteinases. These neurotoxins cause wide spread neuronal cell death in the cerebral cortex and hippocampus[68-70]. Scattered neuronal death in the II and III layers of cerebral cortex as well as in hippocampal CA1 dendritic region is caused by recurrent hypoglycemia of moderate intensity[71,72]. Repetitive mild and moderate hypoglycemia causes cognitive impairment adults probably as a result of deterioration due to synaptic injury. This type of synaptic insult results in its inability to induce or maintain a persistent inhibition of LTP(long term potentiation) as well as facilitation of LTD(long term depression) at hippocampal CA1 (which is important for memory) without an apparent neuronal somatic injuries.

Hence it causes activity-dependent synapse weakening leading to cognitive impairments[74,75].

Executive Dysfunction With Hyperglycemia:

The etiology of executive impairment due to hyperglycemia is multifactorial. At experimental level, hyperglycemia induced detrimental effects on learning, memory as well as executive dysfunction were observed in GK rat[75], Zucker rat (genetic models of Type2Diabetes Mellitus). These rats were evaluated with

1. Morris water maze spatial test
2. inhibitory or active avoidance tasks
3. object discrimination task tests,

They all showed significant impairment in hippocampus and its interconnected structures[75,76]. Chronically elevated blood sugar levels as well as Type2 diabetes mellitus causes blood brain barrier disruption. Hyperglyemia causes modified insulin transporter as well as down regulation of insulin receptors .These Transporters and receptors are present in discrete neuronal populations in the CNS. Further hyperglycemia causes a

decrease in factors like insulin like growth factor 1 and its brain derived neurotropic factor[78-80].

Clinically, adult Diabetes Mellitus patients score low in IQ evaluation tests and have less scores in forward digit span, backward span test. They also show a decline in score levels in memory, comprehension tests. Visual reasoning, pattern analysis, quantitation, are also equally affected. As far as associate learning, psychomotor efficiency, problem solving ability, information processing speed are concerned, they are also equally affected. Many studies reported that executive dysfunction is highly correlated with the level of chronic hyperglycemia. Improvement in performance of executive function testing occurs with improvement in glycemic control[81-85].

The neurophysiological studies observed abnormalities in P300 component of ERPs. Event related potentials are physiological analogue of cognitive testing. The I-III and I-V inter-peak latencies of the auditory brainstem response are prolonged in Type2 diabetes mellitus patients. This prolonged inter-peak is regardless

level metabolic derangement and diabetes mellitus duration[86,87].

The more typical pattern of cognitive deficits in diabetics is suggestive of frontal sub-cortical dysfunction from a micro-vascular insult. Structural brain imaging studies in type 2 diabetics between ages 60 to 65 years revealed an increase in both cerebral atrophy and lacunar infarcts. This pattern of microvascular disease of the brain is characteristically associated with cardiovascular risk factors. In particular this frontal subcortical syndrome manifests with significant executive impairment, motor slowing and mood symptoms, with minimal memory loss. These deficits impact on the individuals' ability to plan, organize, problem solve, reason and also limits their insight[88,89].

Longitudinal and population based studies have implicated type 2 diabetes mellitus as a risk factor for age related cognitive decline and dementia. Cognitive impairments have been evidenced in multiple cross-section, longitudinal, and prospective studies.

Vijayakumar et al in 2010[90] suggested hyperglycemia alters function through a variety of mechanisms including polyol pathway activation, increased formation of advanced glycation end products, diacylglycerol activation of protein kinaseC and increased glucose shunting in the hexosamine pathway leading to changes in cognitive function that have been detected in patients with diabetes.

At the neuroimaging level, continuous arterial spin labeling MRI has shown significant decreased cerebral blood flow resulting in cortical and sub-cortical atrophy[91].

Suggested causes of hyperglycemia induced Executive dysfunction are

1. Diabetic vasculopathy,
2. hyper-lipidemia,
3. hypertension,
4. insulin resistance
5. hyper-insulinemia
6. dysregulation of limbic-hypothalamic-adrenal pituitary axis (LHPA)
7. chronic hyperglycemia induced direct cytotoxicity on neuronal cells.

8. advanced glycation products

9. Inflammatory mediators like cytokines

10. oxidative stress

11. diabetes related depression

Adults Type2diabetes mellitus patiens have higher serum levels of NSE (Neuron specific Enolase – a specific marker of neuronal cell damage).Higher NSE levels correlated well with executive dysfunction This correlation between NSE level and Executive function is regardless of the level of glycemic control, hence, implicating direct Neuronal injury of chronic-hyperglcemia [92].

Pathophysiological Mechanisms of Executive Dysfunction in Diabetes:

Neuroanatomical Changes:

Manschot SM –etal[93] in their study involving 164 older adults, of which113who had type 2 Diabetes mellitus, exhibited up-to 23% cortical atrophy, 12% sub-cortical atrophy more than non-diabetics. Further Diabetics had significantly greater number deep white matter lesions and more numberof infarcts than those without type 2 Diabetes

mellitus. These investigators also noted a small to moderate, but statistically significant deficits in cognitive functions like 1.attention 2.processing speed 3. memory in diabetic mellitus patients.

Glycemic Control and Executive Dyfunction:

Many animal models have shown that increased blood glucose levels may promote the formation of –

1. Advanced glycation products,
2. Reactive oxygen species – S03
3. Activation of polyol / protein kinase C pathway
4. Increased glucose by-passing in to the hexos-amine pathways,
5. Altered Neuro-transmitter functions

Munshi M, etal in 2006[94] demonstrated that glycated hemoglobin levels and measures of working memory have significant inverse relationships. Similar significant inverse relationships exist between HbA1c and measures of visuo-spatial function.

Ha T. Nguyen etal[3] in 2010 examined the association between glycemic control and the executive functioning domain of cognition in ninety-five rural older adults with diabetes found that suggest that poor glycemic control is associated with impairments in performance on composite measures of executive function, and that this relation may be explained by modifiable risk factors for glycemic control such as use of diabetes medication and diabetes knowledge.

INSULIN RESISTANCE AND EXECUTIVE DYSFUNCTION:

It is now known that insulin plays important neuro-trophic roles by interacting with receptors all over the brain, which also includes regions that are thought to be critical for executive functional abilities[95]. Newer evidence are pointing that insulin resistance probably promotes the development of the β-amyloid plaques or inhibit their degradation. β-Amyloid plaques characteristic of Alzheimer disease[96].

VASCULAR DISEASE AND EXECUTIVE DYSFUNCTION:

Newer studies are suggesting that vascular dysfunction could be contributing to executive disturbance. Neuro-pathic and angio-pathic alterations have been noted in the cranial nerves and peripheral nervous system including spinal cord of the diabetic patients. Vasodilation is disrupted by the harmful combination of inadequate cerebral blood flow and hyper-activation of the thromboxane A2 (TX-A2) receptor. The resultant ischemia is propably exacerbated due to associated hyperglycemia in diabetics, thereby providing a favorable environment milieu for damaging agents like lactate and / or glutamate, whose accumulation can cause the neural injury[96,97].

The Rotterdam study[10] (cross-sectional study using dementia as a variable) showed a significant association between diabetes mellitus and dementia, with the strongest association for vascular pattern dementia. Importantly this was found to be independent of education, body mass index, atherosclerosis, smoking, blood pressure or the use

of antihypertensive agents. It was also not explained by cerebral infarcts.

The Hisayama Study[10] (seven year follow-up of 828 diabetic residents aged 65 years and over without baseline dementia) demonstrated an increased risk of vascular dementia.

In a cross-sectional population based study of home bound individuals diabetics had a worse MMSE score: 24/30 vs 25.7/30. Only 50% of diabetic individuals successfully reproduced the pentagon illustration whereas 68% of non-diabetics were successful. However more sensitive tests of executive function such as the Trail B demonstrated significantly worse scores for diabetics[50]. In a large cohort (10963 patients assessed at two separate occasions six years apart) those with diabetes at baseline had a greater decline in scores on two separate executive measures: digit symbol subset and first-letter word fluency. This persisted after controlling for demographic and vascular risk factors, and was also demonstrated when restricted to a younger age group of 47-57 years. In a literature review by Stewart et al. a strong association

between poor verbal fluency scores and type 2 diabetes mellitus was demonstrated[98].

Though it is difficult to elucidate the impact of diabetes mellitus on Executive function, it seems possible that disease-mediated changes in executive function do adversely affect the daily functional abilities in patients with type 2 Diabetes Mellitus.

The purpose of this study is to assess executive function in patients with type 2 Diabetes mellitus in comparison to normal subjects.

AIM

To assess executive functioning in type 2 diabetic patients compared to normal subjects

NULL HYPOTHESIS

There is no difference between the study and control groups, in tests of executive function.

Ethics Committee:

The study was approved by the Institutional Ethical Committee, Madras Medical College vide letter No 20092013.

All subjects (both patients and control group) gave informed consent for participation in written form.

MATERIALS AND METHODS

The study is a cross sectional case control study, conducted at the Rajiv Gandhi Government General Hospital(RGGGH), Chennai. 50 patients attending outpatient department of Diabetology, fulfilling the inclusion criteria were randomly chosen and included in the study. Fifty consenting age, sex, education matched normal people who were relatives of patients attending RGGGH OPD were taken as controls. Both the study population and controls were administered the semi structured proforma. Then GHQ and HAM D was administered to screen for psychiatric symptoms. Those who scored positively were excluded from the study. MMSE was administered as a screening tool for cognition. All diabetes mellitus patients were tested for their blood glucose level before administering the evaluation tests. This was done to avoid hypoglycemia / severe hyperglycemia affecting the executive function assessment.

SUBJECT SELECTION:

50 patients with type II DM attending Diabetalogy OPD in RGGGH

50 normal subjects (attenders of patients attending the OPD)

INCLUSION CRITERIA:

GROUP A:

1. Age 40 – 50 years
2. Type II DM diagnosed as per American Diabetes Association Criteria
3. Giving informed consentCooperative for Cognitive Assessment

GROUP B:

1. Age & gender matched NonDiabetes
2. Giving informed consent Cooperative for Cognitive Assessment

EXCLUSION CRITERIA:

GROUP A:

1. Co-Morbid Medical illness
2. Co-Morbid Psychiatric illness
3. Co-Morbid Neurological illness
4. H/o of substance dependence
5. Intellectual Disabilities
6. Long term benzodiazepine use

GROUP B:

1. Co-Morbid Medical illness
2. Co-Morbid Psychiatric illness
3. Co-Morbid Neurological illness
4. H/o of substance dependence
5. Intellectual Disabilities
6. Long term benzodiazepine use

ASSESSMENTS OF PARAMETERS:

1. Proforma for socio demographic data of study cases and control group
2. Proforma for Diabetes Status
3. Mini Mental State Examination (MMSE)
4. Test for Executive Function:
    a. Digit Span Test
        i. Forward Digit span
        ii. Reverse digit span
    b. Verbal fluency
        i. Letter fluency
        ii. Category Fluency
    c. Trail making test
        i. TMTA
        ii. TMTB
    d. Stroop Test
    e. Wisconsin Card Sorting Test

1. DIGIT SPAN TEST:

The Digit Span Test is a brief test to evaluate the person's cognitive function. It is commonly used in by the physician to rapidly evaluate the normality of patient's cognitive function and mental abilities.

Digit Span Test was originally a component of Wechsler's Intelligence Scale. Wechsler's Intelligence Scale is used evaluate and measure the patient’s IQ (intelligence quotient)

In digit span test the subject is instructed to repeat a series of numbers in the same order as said to them. The evaluator then utters a series of three numerical, such as "4,1, 8." Numbers are said in a clear mono-tone voice, each one a second apart form the next one. The subject then has to repeat back those numerical in the same order as said, back to the evaluator. The next level is to give a series of 4 numbers, such as, "5, 8, 3, 6." Even this time, the subject has repeat those numbers back to the evaluator. This continues in the same sequential series with progressively increasing the series of numerical to 5 and the subject has to repeat the very same numerical back to

the evaluator. The evaluator continues to keep on increasing the series of numerical in order of one every time and then asking the subject to repeat them back to the evaluator as along as the answers are correct and stops when a response is incorrect. Similarly in the backward digit span task the participant needs to reverse the order of the numbers. Of the two the Forward Digit span test is relatively easier when compared to the backward digit span test.

2. VERBAL FLUENCY TEST:

The verbal fluency test is a short screening test that evaluates cognitive function. The Verbal Fluency battery includes tests for Letter and Category fluency. In Verbal fluency test the subject is evaluated for maximum number of word production, within a set time frame, and within a specific constraint, e.g., words starting with the alphabet "S" -- Letter Fluency Test, or name of birds / animals -- Category Fluency test. This is an executive function task where strategies such as clustering can be implemented in order to facilitate word production. In the Letter Fluency test, the subject is give three separate one-minute trials for

the letters F, A, and S. The Category Fluency test is a one-minute trial for a single category like birds which can fly, four legged land animals etc. For Subjects not proficient English, in case of the Letter Fluency Test, 3 letter of their Vernacular language is given. Example – (**அ, க, த)**

3. WISCONSIN CARD SORTING TEST (MILNAR 1963):

Wisconsin card sorting test developed by Milnar in 1963 is used to test the set-shifting ability. It was originally developed to assess abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies. It consists of sixty four tests cards and 4 stimulus cards. Each card is a square of dimensions 8cms by 8cms. The stimuli vary in 3 attributes: color (red, green, yellow, blue), form (triangle, star, cross, circle) and number(1,2,3,4). Of these four stimulus card the first card consist of one red triangle, the second card consist of 2 green stars, the third card consist of 3 yellow crosses and the fourth card consist of 4 blue circles.

The four stimulus cards are placed in front of the subject, with one red triangle placed on the left had side of the subject. Next to it is the card with two green stars, followed by the card with 3 yellow crosses and on the extreme right the card with 4 blue circles. The deck of 64 cards is arranged according to the sequence of presentation given in the test manual and placed to the left side of the subject. The subject is asked to study the cards and match each successive card from the pack to one of the four stimulus card. The subject is told only whether each response is right or wrong and never about the correct sorting principal. Each time the subject places a card according to the sorting principal it is scored starting from 1 and continued serially for consecutive correct responses. After 10 consecutive correct responses, the examiner changes the concept without the knowledge of the subject. The first matching principal is by color then form and finally number. This sequence is repeated.

Scoring in Wisconsin card sorting test:

The scoring is done for the

1. Number of trials administered,

2. Total number of correct responses,

3. Total number of errors,

4. Percent errors,

5. Perseverative responses,

6. Percent perseverative responses,

7. Perseverative errors,

8. Percent perseverative errors,

9. Non-perseverative errors,

10. Percent non perseverative errors, conceptual level responses, Percent conceptual responses, Number of categories completed.

1. Responses that match sorting principle are scored as ***correct*** while incorrect responses are scored as ***errors***.

2. Response is additionally scored as ambiguous or unambiguous

3. When a client persist in responding to a stimulus characteristic that is incorrect, the response is said to

be perseverated to principle and scored as ***Perseverative***

4. Responses not matching to perseverated to principle are scored ***Non perseverative***.

5. The perseverated to principle is established at the beginning of the test the first time the client makes an ***unambiguous error***

6. The first unambiguous response to match the new perseverated to principle is an ***unambiguous perseverative error***

7. ***Number of categories completed*** is simply the number of categories – 10 consecutive correct matches the client completed

8. ***Trials to complete first category*** is total number of trials to successfully complete first category

9. ***Percent perseverative errors*** : density of perseverative errors

10. ***Failure to maintain set*** : error following five or more consecutive correct response before category completion

11. ***Percent Conceptual level response*** : Reflects insight into correct sorting principle

12. ***Learning to learn***: Average change in conceptual efficiency**.**

4. STROOP TEST (ALEXANDER, STUSS,1989):

This test measures the response inhibition ability. Three cards which has 20 rows and 5 columns of either color names or symbol is presented. First card has color names printed in black color, second card has x symbol printed in different colors. And last card has color names blue, green , and red printed in different colors (e.g. red printed in green color).

First card is presented to the subject and asked to read the color words along the column. Then, second card is given and the number of X symbols read is noted. Third card given and the subject has to read the color in which the color names are printed and not the color names. The

time taken to read each card (t1, t2, t3) and the number of errors made is noted. The Stroop effect is calculated as : t3-(t1+t2 / 2).

5. TRAIL MAKING :

Trail Making Test has two parts A and B. Each part consists of 25circles drawn on a plain white paper. In trail making Test-A, the circles are numbered from one to twenty five. The evaluator asks the subject to draw lines connecting the numbers in ascending order. For trail making test - B, the circles are marked with numbers (1 – 13), while remaining circles are labeled with letters (A – L); The evaluator then asks the subject to connect the circles in an order of ascending, but the extra task is to alternate between letters and numbers(i.e., 1-A-2-B-3-C, etc.). The subject is to connect the circles as fast as possible, and without lifting the marker off the paper. Time taken for completion the trail marking is penned in separately for Trail marking test A,B . If an error is done during marking of trail, it is pointed as correction is allowed. But Errors do affect the subject's score in a way, that the correction of errors is included in the completion

time for the task only. Maximum time give for completion of task is 5 minutes and after which the test is called off, as it is unnecessary to continue further.

OPERATIONAL DESIGN:

This was a hospital based study, conducted at Institute of Mental Health, Madras Medical College, Chennai in a cross sectional comparative design, for a period of three months. Approval from the Institutional Ethical Committee, Madras Medical College was obtained.

The sample was chosen from Diabetology outpatient department of RGGGH, Chennai-3 . Patients diagnosed as Type 2 diabetes Mellitus were chosen as cases and attendenders accompanying the patients attending RGGGH, Chennai-3 as controls. All the cases and controls were screened depending on the inclusion and exclusion criteria, were included in the study.

The study subjects were explained about the nature of the study and consent was obtained. Socio demographic details as per proforma collected from cases and controls. Complete physical examination including detailed Neurological evaluation was done. Subsequently, all subjects were given the scales and cognitive assessments as mentioned. Tests were administered in a quiet room in a fixed pre-set order according to standard administration instructions. The time taken was about 1hr to 1hr and 30 minutes. Assessments were carried out in 1-2 sessions, each session not extending beyond 1 hour.

DATA ANALYSIS

STATISTICAL ANALYSIS PLAN:

Comparison of socio demographic data of study and control groups:

Chi square test

Comparison of executive function of study and control groups:

Assessing normality of data for cases and controls

a. Shapiro-Wilk test.

b. Kolmogorov-Smirnov test.

Comparison of neuropsychological scores between cases(study group) and controls.

1. When data distributed Normally

   i. 2 Tailed Students T test

2. For Non-Normative distribution of data

   i. Wilcoxon – Mann-Whitney U test (non-parametric test).

RESULTS

The study is a case control study, cases defined as Type2 Diabetes mellitus and controls as healthy unrelated subjects.

A. Socio-demographic data of cases and controls

With respect to study population (cases), 26(52%) were between than 40 year – 45 years of age, and 24(48%) were between 45 years – 50 years. Sex distribution was, 21(42%) males and 29(58%) females. And 37 (74%) had a secondary education, while 13 (26%) had a degree.

With respect to control group), 28 (56%) were between than 40 year – 45 years of age, and 22(44%) were between 45 years – 50 years. Sex distribution among control was 26 (52%) male and 24 (48%) female. Control group distribution in education was 36 (72%) had a secondary education, while 14 (28%) had a degree.

Table 1 : Socio-Demographic Data

	Cases		Control	
	Number	**Percent**	**Number**	**Percent**
Age				
40 – 45	26	52	28	56
46 – 50	24	48	22	44
Sex : male	21	42	24	48
Female	29	58	26	52
Education :secondary	37	74	36	72
Degree	13	26	14	28
Occupation:				
Unskilled	31	62	28	56
Semiskilled	19	38	20	40
Skilled	0	0	2	4
Marital status : married	50	100	50	100
Domicile: rural	11	22	12	24
Urban	39	78	38	76
SES: Low	6	12	5	10
Middle	44	88	45	90
Religion: Hinduism	40	80	37	74
Christianity Islam	7	14	9	18
	3	6	4	8

Table 2: Comparison of socio-demographic data

Socio-demographic data	Cases(n=50)	Controls(n=50)	$\chi 2$
Age			
40 – 45	26	28	
46 – 50	24	22	0.568
Sex :			
Male	21	24	
Female	29	26	0.546
Education:			
Secondary	37	35	
Degree	13	14	0.752
Occupation :			
Unskilled	31	28	
Semiskilled	19	20	
Skilled	0	2	0.305
Marital status :			
Married	50	50	
Unmarried	0	0	
SES :			
Low	6	7	
Middle	44	43	0.683
Religion :			
Hinduism	40	37	
Christianity	7	9	
Islam	3	4	0.625

No significance seen in chi square testing

Comparison of socio-demographic data of cases and controls shows no significant difference. Hence the two groups are comparable with respect to age, sex distribution, education, occupation, socioeconomic status.

C. ILLNESS CHARACTERISTICS OF DIABETES MELLITUS PATIENTS:

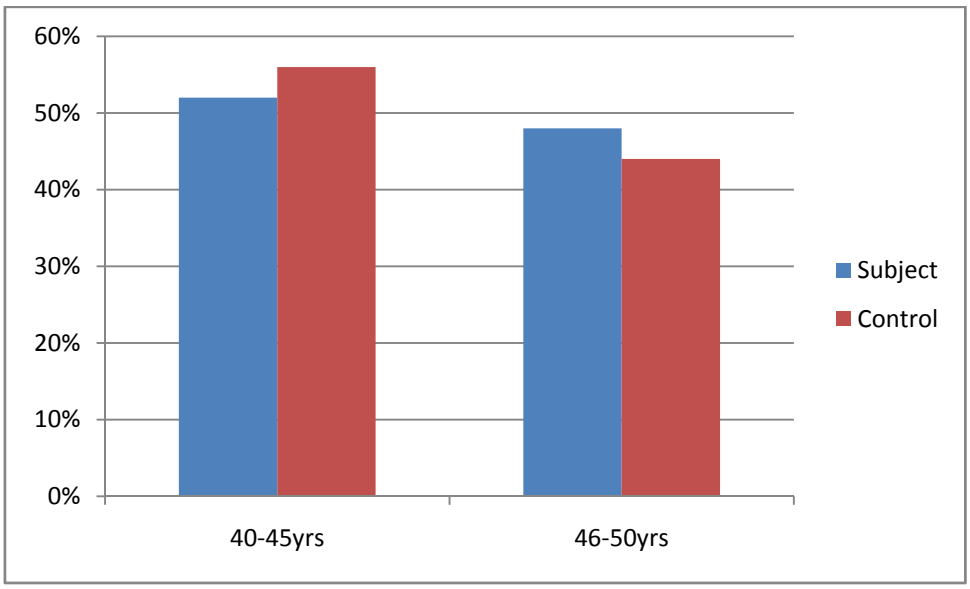
The table 3 below shows the details regarding the illness characteristics of Diabetes Mellitus patients.

Table : 3 Illness characteristics of Diabetes Mellitus patients

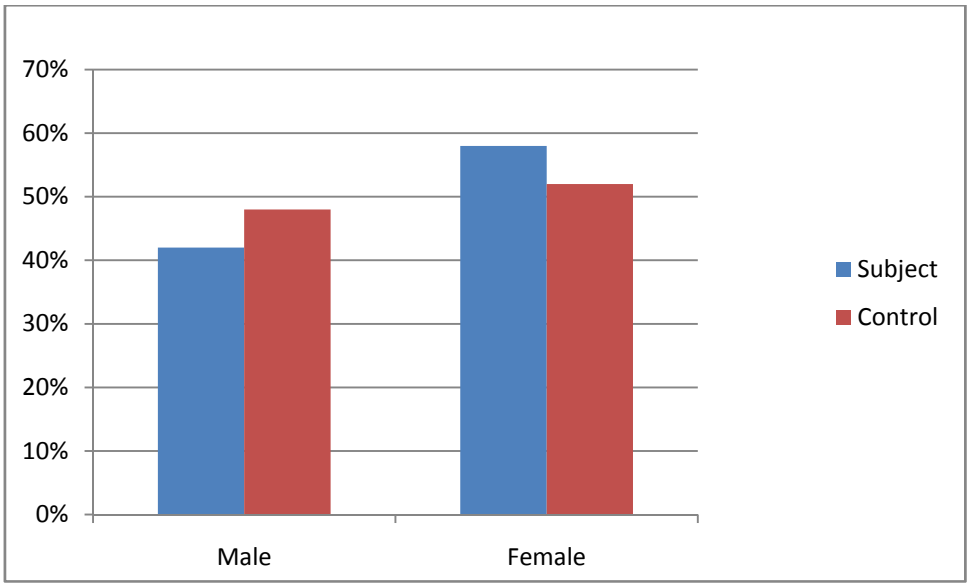
Disease Characteristics	VARIABLES				
Age Of Onset In Yrs	<30	30 – 35	36 – 40	41 – 45	46 – 50
No. Of Patients	2	4	8	30	6
Percentage	4%	8%	16%	60%	12%
Duration Of Illness	0 -12 months	12 – 24 month	24 – 36 months	3 – 5 yrs	>5 yrs
No. Of Patients	2	6	12	20	10
Percentage	4%	12%	24%	40%	20%
Type Of Trearment	Diet / Exer	D&E + OHA	D&E + OHA + Insuin	D&E +I	
No. Of Patients	0	40	10	0	
Percentage	0	80%	20%	0	
Presence Of Complications	NEGATIVE				

The mean age of onset of diabetes mellitus is 41.40 years and the mean duration of illness is < 5 years. There was no major macro / micro vascular complication.

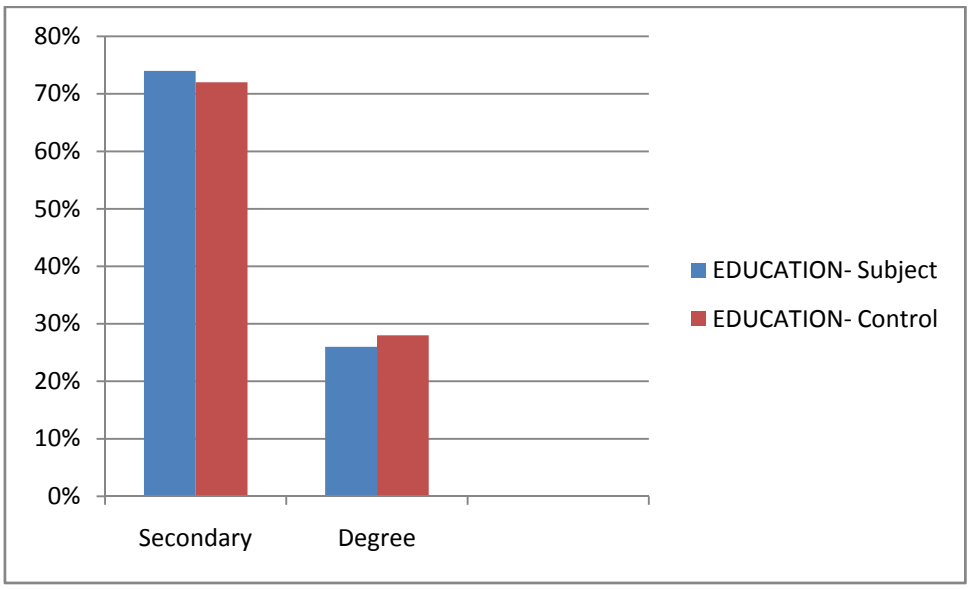
AGE DISTRIBUTION



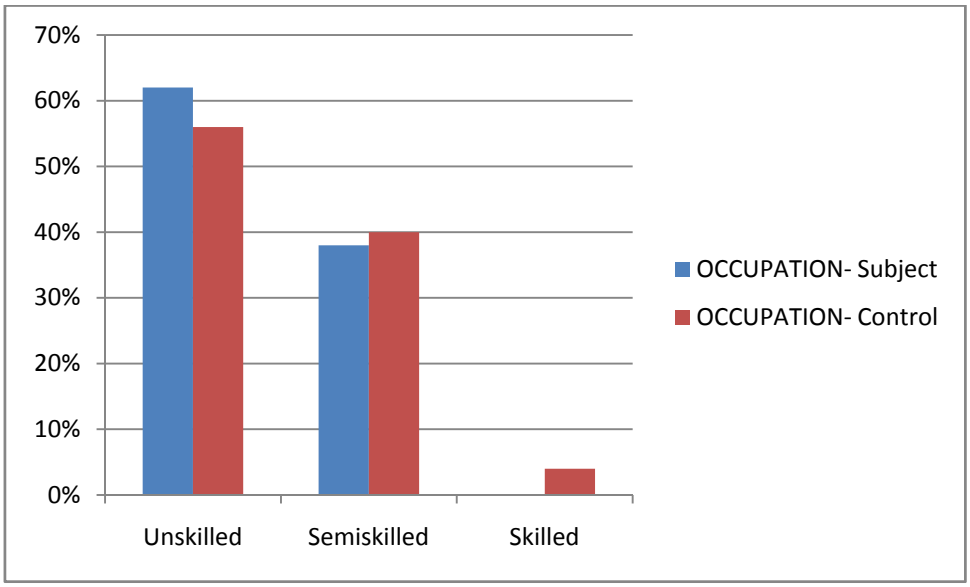
GENDER DISRIBUTION



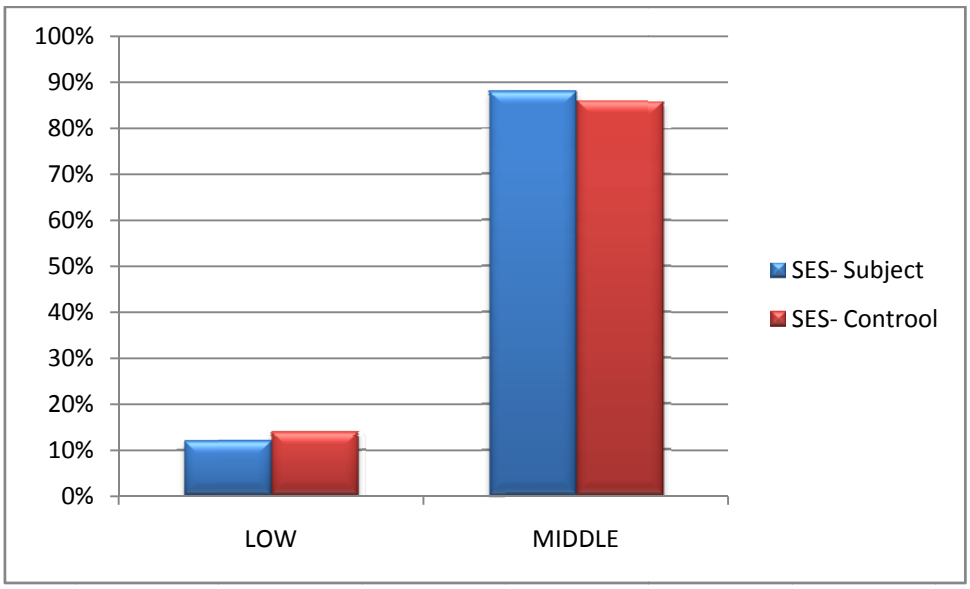
EDUCATION


80%
70%
60%
50%
40%
30%
20%
10%
0%
Secondary
Degree
EDUCATION- Subject
EDUCATION- Control

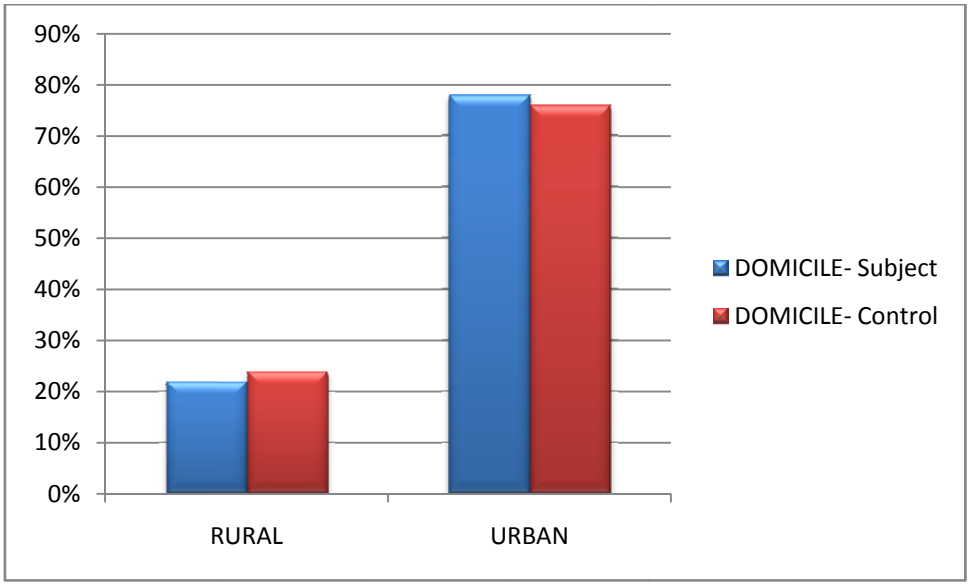
OCCUPATION


70%
60%
50%
40%
30%
20%
10%
0%
Unskilled
Semiskilled
Skilled
OCCUPATION- Subject
OCCUPATION- Control

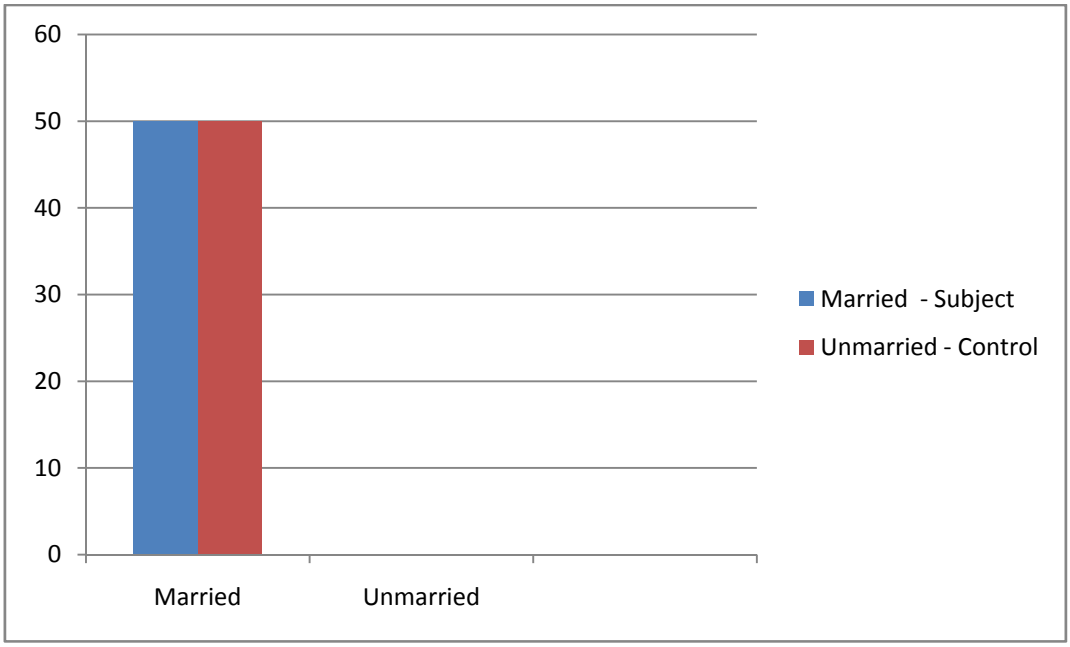
SOCIOECONOMIC STATUS



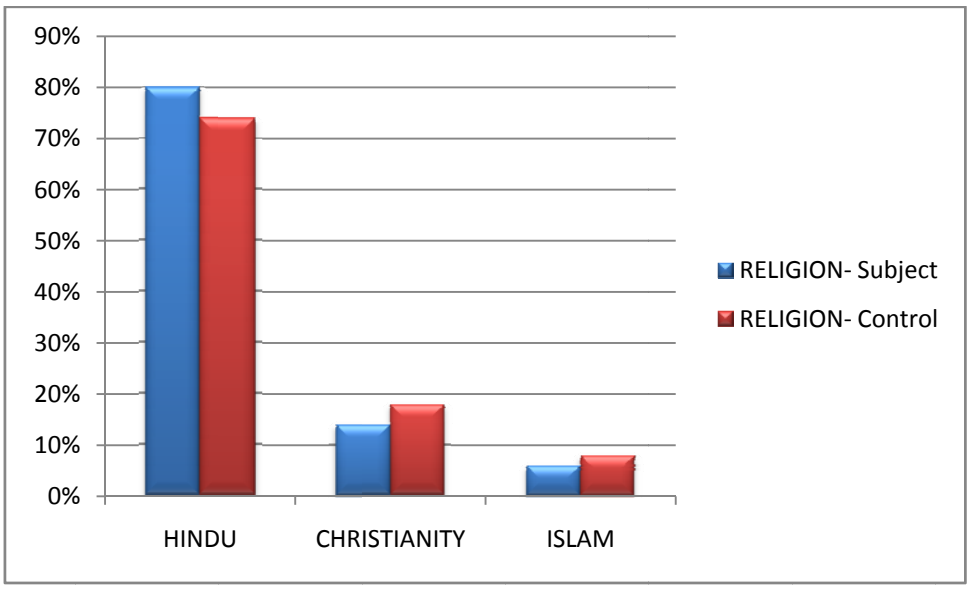
DOMILCILE


90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
RURAL
URBAN
DOMICILE- Subject
DOMICILE- Control

MARITAL STATUS



RELIGION


90%
80%
70%
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50%
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HINDU
CHRISTIANITY
ISLAM
RELIGION- Subject
RELIGION- Control

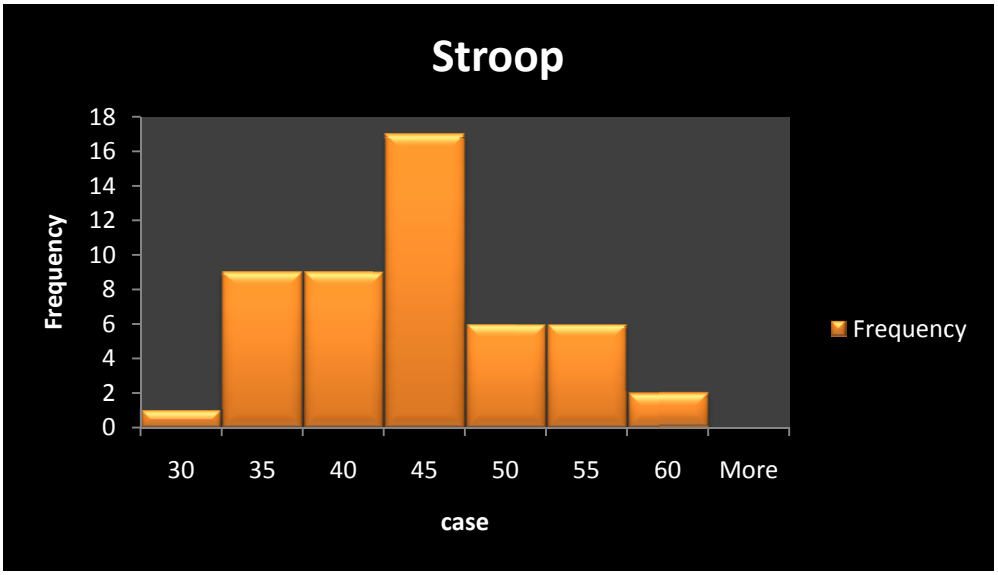
D. ASSESSMENT OF NORMAL DISTRIBUTION OF DATA:

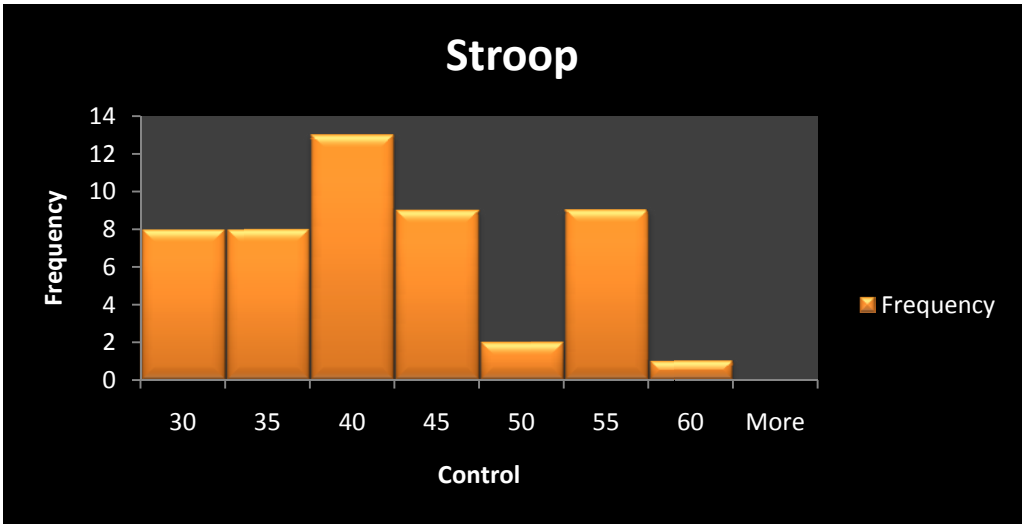
Shapiro-Wilk test is used to assess the normal distribution of data.

Table 4 : Assessing normality of data for cases and controls

Tests of Normality							
CASE_CONT		Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	Df	Sig	Statistic	Df	Sig
STROOP TEST	CASE	0.61	50	0.15	0.950	50	0.114
	CONTROL	0.07	50	0.027	0.904	50	0.002

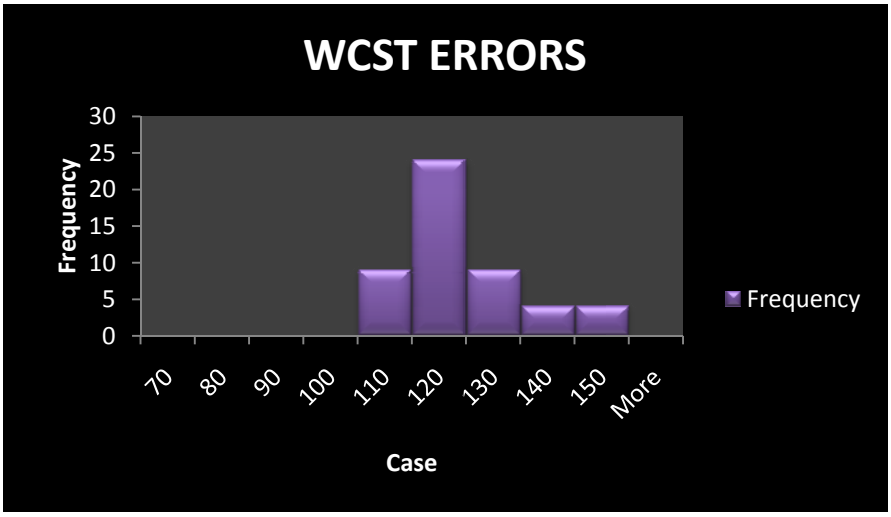
Shapiro-Wilk test, which is a standard test used for assessing the normal distribution of data. The above table 4 gives the normality testing for cases and controls for Stroop test. The results were significant (0.114) for cases but not significant for controls (0.002). This means the data falls under normal distribution curve for cases but not controls, as depicted pictorially in the histogram.

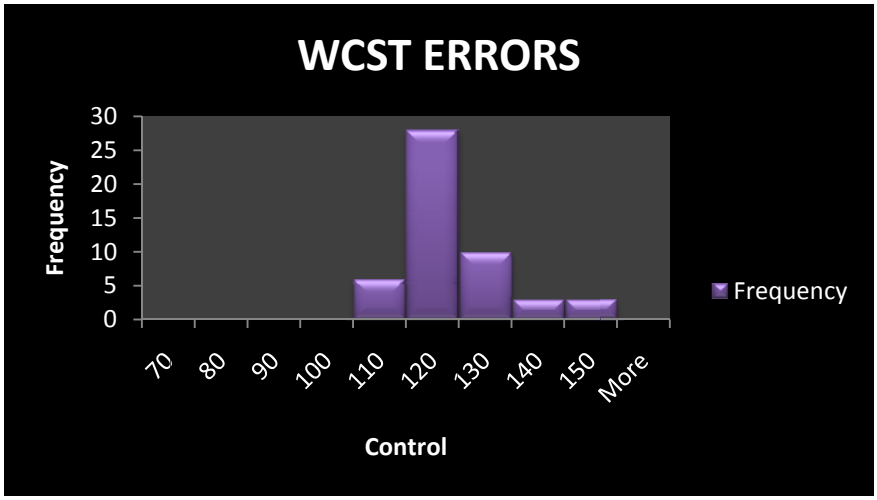

Stroop
Frequency
18
16
14
12
10
8
6
4
2
0
30
35
40
45
50
55
60
More
case
Frequency


Stroop
Frequency
14
12
10
8
6
4
2
0
30
35
40
45
50
55
60
More
Control
Frequency

Similarly for Wisconsin card sorting test score of errors (WCST), Shapiro-Wilk test shows normal distribution for cases but Non-normal distribution for controls, which also depicted in the histogram.

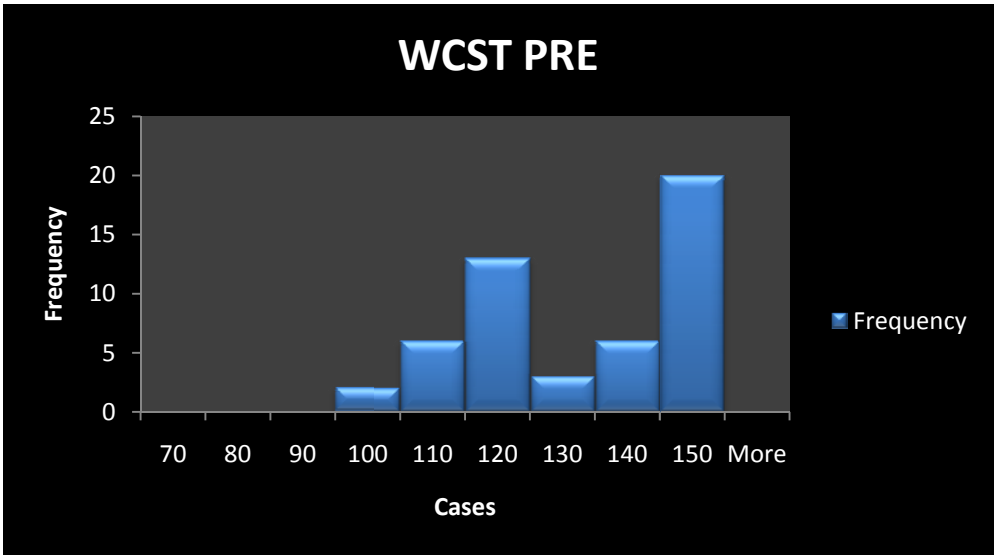
Test for normality							
CASE_CONT		Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	Df	Sig	Statistic	Df	Sig
WCST ERRORS	CASE	0.30	50	0.15	0.962	50	0.229
	CONTROL	0.01	50	0.01	0.887	50	0.001

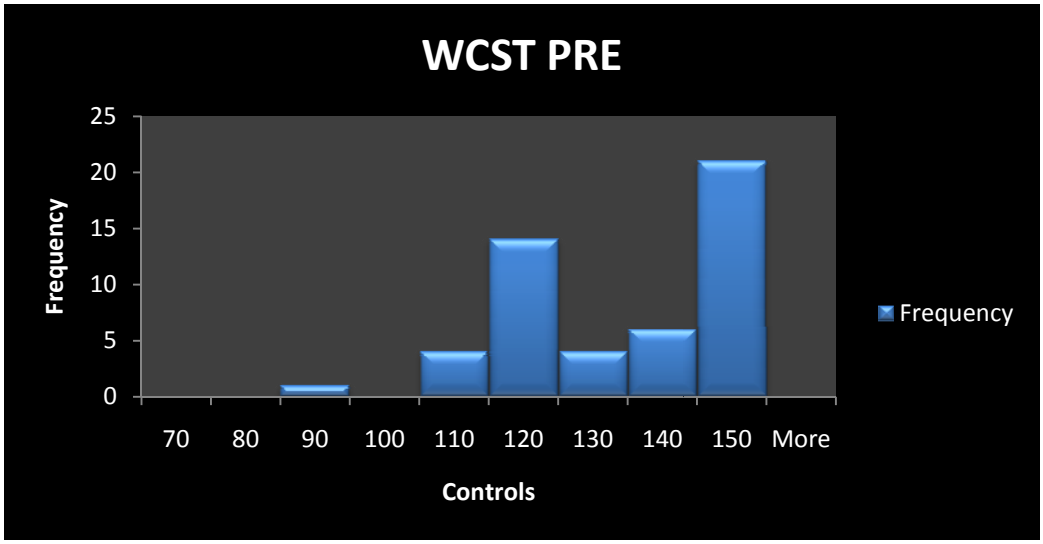

WCST ERRORS
Frequency
30
25
20
15
10
5
0
70
80
90
100
110
120
130
140
150
More
Case
Frequency


WCST ERRORS
Frequency
30
25
20
15
10
5
0
70
80
90
100
110
120
130
140
150
More
Control
Frequency

Tests of Normality							
CASE_CONT		Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	Df	Sig	Statistic	Df	Sig
WCST PRE	CASE	0.03	50	0.01	0.881	50	0.001
	CONTROL	0.01	50	0.01	0.810	50	0.001

The next data for Perseverative Response Errors shows non-normal distribution for cases and controls.


WCST PRE
25
20
15
10
5
0
Frequency
70
80
90
100
110
120
130
140
150
More
Cases
Frequency


WCST PRE
25
20
15
10
5
0
Frequency
70
80
90
100
110
120
130
140
150
More
Controls
Frequency

E. COMPARISON OF NEUROPSYCHOLOGICAL SCORES BETWEEN CASES (STUDY GROUP) AND CONTROLS:

A total of 5 neuropsychological tests (Digit span (forward, backward), Verbal Fluency (Letter and Category Fluency), Trail making test – A&B, Stroop test, and Wisconsin card sorting test, were administered to cases and controls, yielding 17 scores. Higher the scores better the performance, lower the scores, poorer the performance for Digit Span and Verbal Fluency. For trail making test the time taken to complete is scored in seconds. Higher the score, poorer the performance. For Stroop test, Stroop effect is calculated, higher the score poorer the performance. The standard scores from Wisconsin card sorting test manual are entered for each parameter. Higher the score better the performance.

The Wilcoxon – Mann-whitney U test (non parametric test) is used for comparison of neuropsychological test scores of cases and controls.

DIGIT SPAN TEST

Table 5: Forward digit span

FORWARD DIGIT SPAN								
TESTS	CAES (n=50		CONTROLS (n=50)		MANN-WHITNEYU	WILCOXONW	Z	SIGNIFICANT2TAILED
	MEAN	SD	MEAN	SD				
FDS	6.439	0.884	6.64	1.064	1104.5	2654.5	1.174	.240

For Forward Digit span test, cases group reproduced less Numbers (mean - 6.439, SD - 0.884) compared to controls (mean - 6.64, SD - 1.064). The Mann-whitney Uscore, Wilcoxon W and Z scores comparing two groups are 1104.5(U), 2654.5 (W), 1.174 (Z) respectively. And the test scores are statistically not significant at p – 0.24.

Table 6: Backward digit span

TESTS	CASES (n=50)		CONTROL		MANN-WHITNEYU	WILCOXON W	Z	SIGNIFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
BDS	4.36	0.525	4.52	0.667	1070.0	2345.0	1.241	0.214

For Backward Digit span test, cases group reproduced less Numbers (mean - 4.36, SD - 0.525) compared to controls (mean - 4.52, SD - 0.667). The Mann-whitney Uscore, Wilcoxon W and Z scores comparing two groups are 1070(U), 2345 (W), 1.241 (Z) respectively. And the test scores are statistically not significant at p – 0.214.

VERBAL FLUENCY

Table 7: Letter Fluency

LETTER FLUENCY								
TESTS	CASES (n=50)		CONTROLS (n=50)		MANN-WHITNEYU	WILCOXONW	Z	SIGNIFICANT2 TAILED
	MEAN	SD	MEAN	SD				
LF	41.58	3.540	42.22	2.772	1099.5	2374.5	1.038	0.303

For Letter Fluency test, cases group produced less words (mean - 41.58, SD - 3.540) compared to controls (mean - 42.22, SD - 2.772). The Mann-whitney U score, Wilcoxon W and Z scores comparing two groups are 1099.5(U), 2374.5 (W), 1.038 (Z) respectively. And the test scores are statistically not significant at p – 0.30.

Table 8: Category Fluency

CATEGORY FLUENCY								
TESTS	CASES (n=50)		CONTROLS (n=50)		MANN WHITN EYU	WILC OXON W	Z	SIGN IFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
CF	13.16	1.166	13.46	1.092	1070.5	2345.5	1.237	0.218

For Category Fluency test, cases group produced less words (mean - 13.16, SD - 1.166) compared to controls (mean - 13.46, SD - 1.092). The Mann-whitney U score, Wilcoxon W and Z scores comparing two groups are 1070.5(U), 2345.5 (W), 1.237 (Z) respectively. And the test scores are statistically not significant at p – 0.218

TRAIL MAKING TEST

Table 9: Trail making test A

TMTA								
TESTS	CASES (n=50)		CONTROLS (n=50)		MANN WHITNEY U	WILCO XONW	Z	SIGN
TMTA	MEAN	SD	MEAN	SD				
SECS	32.13	3.658	30.15	3.786	899.5	2174	-2.416	0.015

Trail making test A tests the speed of a subject. In this,cases took longer time to complete the task (mean 32.13, SD 3.658) when compared to the control group (mean 30.15, SD 3.786). Oncomparing the performance of two groups, there was significant difference with $p < 0.015$; the Mann-whitney U score is 899.5, Wilcoxon W is 2174.000 and Z score is -2.416.

Table 10: Trail making test B

TMTB								
TESTS	CASES (n=50)		CONTROLS (n=50)		MANN WHITNEYU	WILCOXONW	Z	SIGNIFICANT2TAILED
TMTB	MEAN	SD	MEAN	SD				
SECS	79.679	14.808	71.18	10.03	803	2078	-3.082	0.002

Trail making test B tests the set-shifting ability of a subject. In this, cases took longer time to complete the task (mean 79.679, SD 14.808) when compared to the control group (mean 71.18, SD 10.03). On comparing the performance of two groups, there was significant difference with $p < 0.002$; the Mann-whitney U score is 98.000 , Wilcoxon W is 563.000 and Z score is -3.2078.

STROOP TEST

Table 11: stroop test

STROOP								
TESTS	CASES		CONTROLS (n=50)		MANN WHITN EYU	WILCO XON W	Z	SIGNIFIC ANT2 TAILED
STROOP	MEAN	SD	MEAN	SD				
SECS	42.78	7.197	40.12	8.263	972.5	2251.5	-1.855	0.059

Stroop test is used to test the response inhibition of executive functioning. It scores the time taken to complete each card and the number of errors made in each. The Stroop effect calculated using the time factor, shows cases (mean 42.78, SD 7.197)took more time to complete the task compared to the control group (mean 40.12, SD 8.263). Though the errors were not used in computation of Stroop effect, cases made more errors compared to the controls in third card. The scores in the Mann-whitney U is 972.5, Wilcoxon W is 2251.5 and Z score is -1.855 ; the difference in their performance was not statistically significant $p<0.059$.

WISCONSIN CARD SORTING TEST:

Wisconsin card sorting test (WCST) is the gold standard test for executive function testing. The raw scores for each parameter were noted and their corresponding standard scores entered from test manual. The overall performance was marginally better in control group compared to cases who made more number of errors (total and perseverative) and perseverative responses. So the standardized scores were marginally low in cases compared to controls.

Table 13: Wisconsin card sorting test

W ERRORS								
TESTS	CASES		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
ERROR	118.28	9.272	119.00	9.64	1222	2497.0	0.193	0.849

WISCONSIN PERCENTAGE OF ERRORS								
TESTS	CASES		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
ERROR%	111.58	10.862	112.88	11.527	1177	2452.0	0.503	0.617

WISCONSIN PRESEVATIVE RESPONSE								
TESTS	CASES		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFICANT2 TAILED
	MEAN	SD	MEAN	SD				
PE	128.68	16.739	130.22	15.58	1184	2459.0	0.455	0.652

WISCONSIN PRESEVATIVE RESPONSE PERCENTAGE								
TESTS	CASES		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFICANT2 TAILED
	MEAN	SD	MEAN	SD				
PR%	118.22	21.539	121.10	20.76	1139	2414.0	0.765	0.447

WISCONSIN PRESEVATIVE ERRORS								
TESTS	CASES		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
PE	128.86	15.616	130.12	14.70	1202	2477.0	0.331	0.741

WISCONSIN PRESEVATIVE ERROR PERCENTAGE								
TESTS	CASES		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
PE%	118.04	19.665	119.54	18.72	1190.5	2465.5	0.410	0.6818

WISCONSIN NON-PRESEVATIVE ERRORS								
TESTS	CASES		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
NPE	116.38	11.96	115.42	10.13	1237	2512.0	-0.090	0.928

WISCONSIN NON-PRESEVATIVE ERROR PERCENTAGE								
TESTS	CASES (n=50)		CONTROLS (n=50)		MANN WHITNEYU	WILCOXON W	Z	SIGNIFIC ANT2 TAILED
	MEAN	SD	MEAN	SD				
NPE%	110.66	11.829	109.92	11.02	1212	2487	-0.262	0.794

WISCONSIN CLR								
TESTS	CASES (n=50)		CONTROLS (n=50)		MANN WHIT NEYU	WILC OXON W	Z	SIGNIF 2 TAILED
	MEAN	SD	MEAN	SD				
CLR	50.52	5.559	50.14	4.738	1141	2416	0.751	0.453
CLR%	109.68	12.005	110.02	10.822	1209	2484	0.283	0.779
CC	5.08	0.695	5.14	0.670	1194	2469.0	0.386	.703

The scores on comparison of WCST errors are, Mann-whitney U 1222, Wilcoxon W 2497.500 and Z score is 0.193, p – 0.849 ; The scores on comparison of WCST percent errors are, Mann-whitney U 1177, Wilcoxon W 2452 and Z score 0.503, p – 0.617 ; similarly for WCST perseverative response the scores are, Mann-whitney U 1184, Wilcoxon W 2459 and Z score is 0.455 p – 0.652; for percent perseverative response Mann-whitney U 1139, Wilcoxon W 2414 and Z score is 0.765, p – 0.447.

All these tests did not show statistically significance difference between the two groups.

The scores on comparison of WCST perseverative errors are Mann-whitney U 1201, Wilcoxon W 2477 and Z score 0.331, p – 0.741 . The scores for WCST percent perseverative errors are Mann-whitney U 1190.5, Wilcoxon W 2465.5 and Z score 0.410 p – 0.681. Scores for WCST non-perseverative errors are, Mann-whitney U 1237, Wilcoxon W 2512 and Z score -0.090 p – 0.928; for WCST percent non perseverative errors , Mann-whitney U 1212, Wilcoxon W 2487 and Z score -0.262 p

– 0.762; all the test scores were not statistically significant.

The comparison of scores for conceptual level response Mann-whitney U 1141, Wilcoxon W 2416, Z score -4.947; percent conceptual level response Mann-whitney U 105.000, Wilcoxon W 570.000 , Z score 0.751 p – 0.453 ; categories completed, Mann-whitney U 1189, Wilcoxon W 2469.000 , Z score 0.386 p – 0.703. All the test were not statistically significant.

DISCUSSION:

The devastating affect of type 2 diabetes mellitus on cardio-vascular, kidney, retinal, and peripheral nerves have been extensively studied and adequately well documented. But, newer evidence are suggesting that older adults with diabetes mellitus exhibit significant impairment in planning, coordinating, sequencing, as well as monitoring of cognitive operations, which are the pillars of executive function.

Epidemiological studies suggest that diabetes mellitus is a stronger risk factor for Alzheimer disease. Recent research studies following large groups over many years suggest that adults with type 2 diabetes have a higher risk of later developing Alzheimer′s, and the risk effects are stronger when diabetes occurs mid-life than in late life.

Thes study aimed at assessing executive functioning in type2 diabetes mellitus patients

aged between 40 -50 years controlled for factors that affect cognitive functioning, compared to Non-diabetic controls. Age group of 40-50 years was taken mainly to avoid any age related cognitive deficits. Formal education of at least 8th standard was applied so that the subjects could understand the tests and perform.

In the diabetic patients, overall duration of disease was less than five years. They were on regular follow-up. Their blood sugar was controlled by diet, exercise, and oral Hypoglycemic drug in all patients. In 20% of diabetic patients insulin was also required to achieve. The diabetes mellitus patient were all aware of their chronic medical condition. Hence they calibrated and titrated their personal health care and checkup according to it. But they were not in any way grossly inferior in major health, sensory, and physio-psychological characteristics.

Similar criteria was applied for selection of control group and both groups were administered

structured questionnaires to identify and exclude the presence of any psychiatric disease. Subjects with history of any neurological illness or substance dependence were excluded to remove any confounding effects. The socio-demographic data of the study and control groups were matched with respect to age, sex, education and occupation.

Executive Function was tested using a battery of test -

a. Forward Digit span
b. Reverse digit span
c. Letter fluency
d. Category Fluency
e. Trail making test A & B
f. Wisconsin Card Sorting Test
g. Stroop Test

On analysis of performance executive test function battery, no significant difference, observed between the two groups, and the diabetic

group had an equivalent MMSE score compared to control group.

The overall trend of diabetes-related deficits in performance(poor scores), discrepancy in the results are not uncommon (Nilsson, 2006). In our study we found that here was no significant difference between diabetic and non-diabetic group in case digit span, verbal fluency, stroop test and WCST.

There was a statistically significant difference between case and control group in Trail Making Test. There was average difference of 8 seconds between diabetic and non- diabetics. The Stroop test showed a similar slowing in diabetics of 3 seconds bot not statistically significant. Diabetes mellitus related slowing in a number of speed based tasks were observed in many previous studies. Those evaluating basic reaction time or perceptual speed are the most affected. (Arvanitakis, etal 2006; Awad et al., 2004; Fontbonne, etal 2001; Messier in 2005).

The digit span test did not show much difference between case and control group. The verbal fluency was also within normal limit in diabetics compared to the non-diabetics. The Wisconsin card sorting test - [WCST (perseveration), B: WCST (category) and C: WCST (conceptual responses)] also did not vary significantly between diabetic group and non-diabetic group. The diabetes mellitus - associted performance deficitsin executive function was observed in some (but not all) studies (Awad et al., 2004; Messier, 2005; Ryan & Geckle, 2000; Stewart & Liolitsa, 1999). It may be because ofexecutive functions, involvement in multiple undermining processes or dimensions (de Frias, Dixon, & Strauss, 2006; Miyake, Freidman,Emerson, Witzki, & Howerter, 2000).

Nilsson (2006), suggested not all aspects of cognition may be equally or coincidentally affected by Type 2 diabetes, at least in relatively mild to-moderate cases. Executive Dysfunction

could be attributed to diabetes mellitus severity,its neurological sequelae or due to other associated multiple co-morbid conditions.

Wong etal(2002) showed that diabetic retinopathy is independently associated with poor cognitive functioning. Cerebral Micro-vascular disease may contribute to cognitive impairment. Prospective multicentric and multi-national studies like LADIS or randomized studies such as PROSPER highlighted diabetes as an independent risk factor for cognitive impairment in elderly individuals over 70 years.

Type2 Diabetes mellitus associated neurological mechanisms is compounded by many other co-morbid conditions which can, compound, confound ,as well as exaggerate and exacerbate the Executive dysfunction due to diabetes mellitus. Important among these associated co-morbidities are: neurological / psychiatric affections, hypertension, cardio-vascular and cerebro-vascular diseases, as well as drug usage.(e.g., Arvanitakis

et al, 2006; Jacobson et al.2007; Robertson et al,1986; Vanhanen et al., 1998; van Harten et al., 2007; Xu, Qiu, et al, 2004).

Hence, in my study we used a series of cognitive and physical health-related exclusionary criteria for subject selection to the case group. Our study group were between 40 -50 years age group, with a duration of disease less than or equal to five years, without any macro-vascular complications. This study group didn't show a significant executive dysfunction compared to previous studies probably due to relatively recent onset disease and a younger population group. My diabetes mellitus studr group with a N- 50 is well within the acceptable range of comparable former neuropsychological studies.

CONCLUSION:

Executive functioning in patients with Type 2 diabetes mellitus was comparable to that of control group. Though Trail making test, showed a statistical difference between diabetics and non-diabetic, it was still within the normative Range for the particular age group. Validation of these conclusion requires a larger group and prospective longitudinal study. Future follow up assessment is essential to see how the Cognitive dysfunction would develop in our patients over a period of time and whether they will also develop problems in their executive functions and information processing abilities as concluded by other studies.

LIMITATIONS:

- The study sample size in both cases and controls groups is low which might reduce the power of study.
- This is a cross sectional study assessing the cognitive functioning which might bring about individual variations during one assessment.
- Long term glycemic control(HbA1c) were not incorporated.

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APPENDIX 1

PROFORMA

1. Name :

2. Age

3. Sex :

4. Occupation :

5. Marital status : Married / Unmarried

6. Domicile : Rural / Urban

7. Educational status: Primary / secondary / degree

8. Socio economic status: low / middle / high

9. Religion : Hinduism / Christianity / Islam

10. Relation to patient :

APPENDIX 2

PROFORMA-CLINICAL CHARACTERISTICS OF TYPE2 DIABETES MELLITUS PATIENTS

1.Name :

2.Age of onset of illness :

3.Duration of illness :

4. Type of treatment :

- Diet and Exercise
- Diet And Exercise + Oral Hypoglycemic Drugs
- Diet And Exercise + Oral Hypoglycemic Drugs + Insulin
- Diet and Exercise + Insulin

5. Presence of Complication:

APPENDIX 3

General Health Questionnaire:

We want to know how your health has been in general over the last few weeks. Please read the questions below and each of the four possible answers. Circle the response that best applies to you. Thank you for answering all the questions.

Have you recently:

1. been able to concentrate on what you're doing?

better than usual same as usual less than usual much less than usual

(0) (1) (2) (3)

2. lost much sleep over worry?

Not at all no more than usual rather more than usual much more than usual

(0) (1) (2) (3)

3. felt that you are playing a useful part in things?

more so than usual same as usual less so than usual much less than usual

(0) (1) (2) (3)

4. felt capable of making decisions about things?

more so than usual same as usual less than usual much less than usual

(0) (1) (2) (3)

5. felt constantly under strain?

Not at all no more than usual rather more than usual much more than usual

(0) (1) (2) (3)

6. felt you couldn't overcome your difficulties?

Not at all no more than usual rather more than usual much more than usual

(0) (1) (2) (3)

7. been able to enjoy your normal day to day activities?

more so than usual same as usual less so than usual much less than usual

(0) (1) (2) (3)

8. been able to face up to your problems?

more so than usual same as usual less than usual much less than usual

(0) (1) (2) (3)

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9. been feeling unhappy or depressed?

not at all no more than usual rather more than usual much more than usual

(0) (1) (2) (3)

10. been losing confidence in yourself?

not at all no more than usual rather more than usual much more than usual

(0) (1) (2) (3)

11. been thinking of yourself as a worthless person?

not at all no more than usual rather more than usual much more than usual

(0) (1) (2) (3)

12. been feeling reasonably happy, all things considered?

more so than usual same as usual less so than usual much less than usual

(0) (1) (2) (3)

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General Health Questionnaire Scoring

Scoring – Likert Scale 0, 1, 2, 3 from left to right.

12 items, 0 to 3 each item

Score range 0 to 36.

Scores vary by study population.1. Scores about 11-12 typical. 2. Score >15 evidence of distress 3. Score >20 suggests severe problems and psychological distress

APPENDIX 4

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

Patient Name _____ Today's Date _____

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

1. DEPRESSED MOOD
(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)
0 = Absent
1 = Sadness, etc.
2 = Occasional weeping
3 = Frequent weeping
4 = Extreme symptoms

2. FEELINGS OF GUILT
0 = Absent
1 = Self-reproach, feels he/she has let people down
2 = Ideas of guilt
3 = Present illness is a punishment; delusions of guilt
4 = Hallucinations of guilt

3. SUICIDE
0 = Absent
1 = Feels life is not worth living
2 = Wishes he/she were dead
3 = Suicidal ideas or gestures
4 = Attempts at suicide

4. INSOMNIA - Initial
(Difficulty in falling asleep)
0 = Absent
1 = Occasional
2 = Frequent

5. INSOMNIA - Middle
(Complains of being restless and disturbed during the night. Waking during the night.)
0 = Absent
1 = Occasional
2 = Frequent

6. INSOMNIA - Delayed
(Waking in early hours of the morning and unable to fall asleep again)
0 = Absent
1 = Occasional
2 = Frequent

7. WORK AND INTERESTS
0 = No difficulty
1 = Feelings of incapacity, listlessness, indecision and vacillation
2 = Loss of interest in hobbies, decreased social activities
3 = Productivity decreased
4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).

8. RETARDATION
(Slowness of thought, speech, and activity; apathy; stupor.)
0 = Absent
1 = Slight retardation at interview
2 = Obvious retardation at interview
3 = Interview difficult
4 = Complete stupor

9. AGITATION
(Restlessness associated with anxiety.)
0 = Absent
1 = Occasional
2 = Frequent

10. ANXIETY - PSYCHIC
0 = No difficulty
1 = Tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude
4 = Fears

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

☐ 11. ANXIETY - SOMATIC
Gastrointestinal, indigestion
Cardiovascular, palpitation, Headaches
Respiratory, Genito-urinary, etc.
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

☐ 12. SOMATIC SYMPTOMS - GASTROINTESTINAL
(Loss of appetite , heavy feeling in abdomen; constipation)
0 = Absent
1 = Mild
2 = Severe

☐ 13. SOMATIC SYMPTOMS - GENERAL
(Heaviness in limbs, back or head; diffuse backache; loss of energy and fatiguability)
0 = Absent
1 = Mild
2 = Severe

☐ 14. GENITAL SYMPTOMS
(Loss of libido, menstrual disturbances)
0 = Absent
1 = Mild
2 = Severe

☐ 15. HYPOCHONDRIASIS
0 = Not present
1 = Self-absorption (bodily)
2 = Preoccupation with health
3 = Querulous attitude
4 = Hypochondriacal delusions

☐ 16. WEIGHT LOSS
0 = No weight loss
1 = Slight
2 = Obvious or severe

☐ 17. INSIGHT
(Insight must be interpreted in terms of patient's understanding and background.)
0 = No loss
1 = Partial or doubtfull loss
2 = Loss of insight

TOTAL ITEMS 1 TO 17: _____
0 - 7 = Normal
8 - 13 = Mild Depression
14-18 = Moderate Depression
19 - 22 = Severe Depression
≥ 23 = Very Severe Depression

☐ 18. DIURNAL VARIATION
(Symptoms worse in morning or evening. Note which it is.)
0 = No variation
1 = Mild variation; AM ( ) PM ( )
2 = Severe variation; AM ( ) PM ( )

☐ 19. DEPERSONALIZATION AND DEREALIZATION
(feelings of unreality, nihilistic ideas)
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

☐ 20. PARANOID SYMPTOMS
(Not with a depressive quality)
0 = None
1 = Suspicious
2 = Ideas of reference
3 = Delusions of reference and persecution
4 = Hallucinations, persecutory

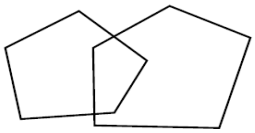
☐ 21. OBSESSIONAL SYMPTOMS
(Obsessive thoughts and compulsions against which the patient struggles)
0 = Absent
1 = Mild
2 = Severe

APPENDIX 5

MINI MENTAL STATE EXAMINATION (MMSE)

Patient's name:

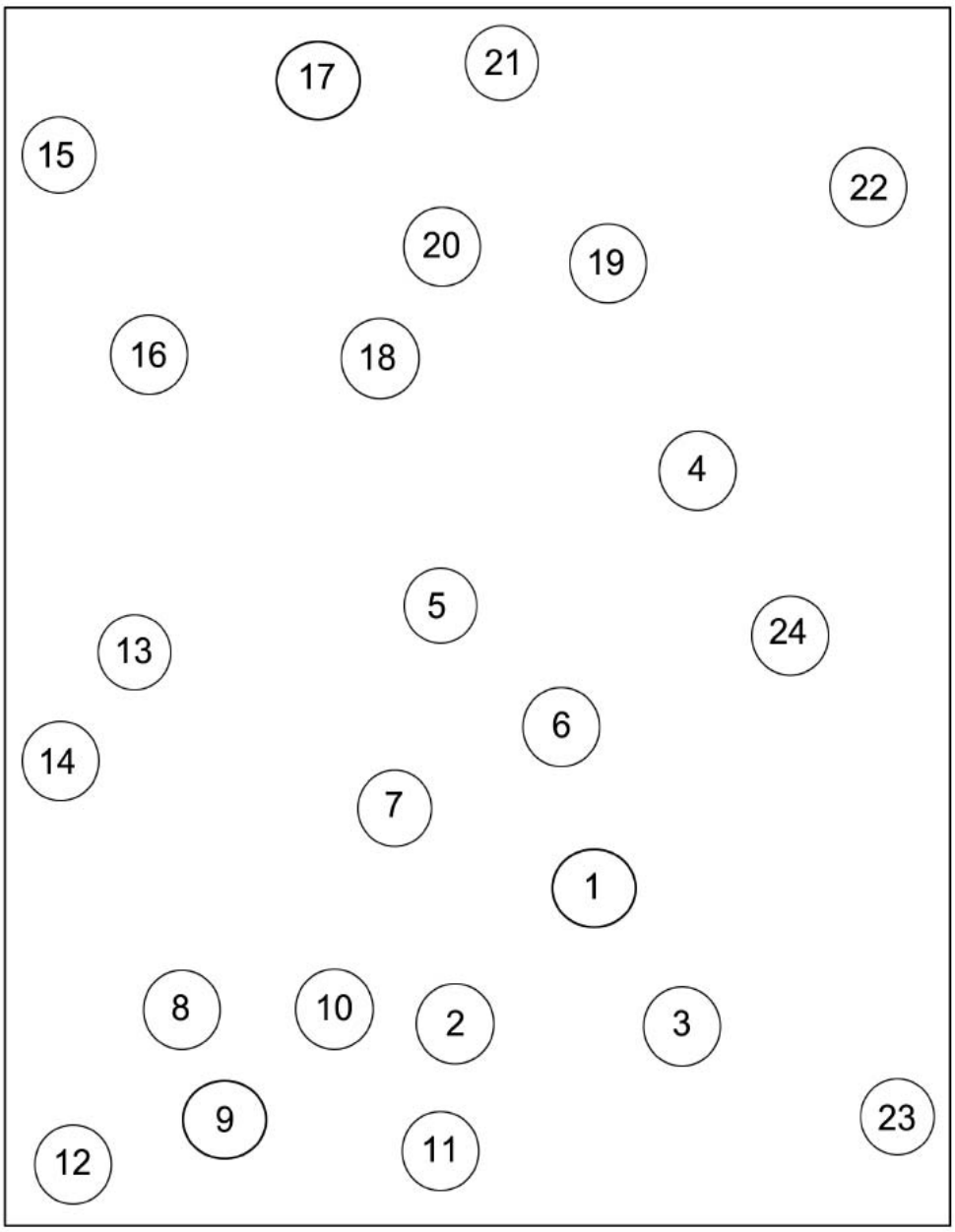
Hospital number:

ONE POINT FOR EACH ANSWER	DATE			
ORIENTATION				
Year Month Day Date Time	____/5	____/5	____/5	____/5
Country Town District Hospital Ward	____/5	____/5	____/5	____/5
REGISTRATION				
Examiner names 3 objects (eg apple, table, penny) Patient asked to repeat (1 point for each correct). THEN patient to learn the 3 names repeating until correct.	____/3	____/3	____/3	____/3
ATTENTION AND CALCULATION				
Subtract 7 from 100, then repeat from result. Continue 5 times: 100 93 86 79 65 Alternative: spell "WORLD" backwards - dlrow.	____/5	____/5	____/5	____/5
RECALL				
Ask for names of 3 objects learned earlier.	____/3	____/3	____/3	____/3
LANGUAGE				
Name a pencil and watch.	____/2	____/2	____/2	____/2
Repeat "No ifs, ands, or buts".	____/1	____/1	____/1	____/1
Give a 3 stage command. Score 1 for each stage. Eg. "Place index finger of right hand on your nose and then on your left ear".	____/3	____/3	____/3	____/3
Ask patient to read and obey a written command on a piece of paper stating "Close your eyes".	____/1	____/1	____/1	____/1
Ask the patient to write a sentence. Score if it is sensible and has a subject and a verb.	____/1	____/1	____/1	____/1
COPYING Ask the patient to copy a pair of intersecting pentagons: 	____/1	____/1	____/1	____/1
TOTAL	____/30	____/30	____/30	____/30

APPENDIX 6

Trail making test A

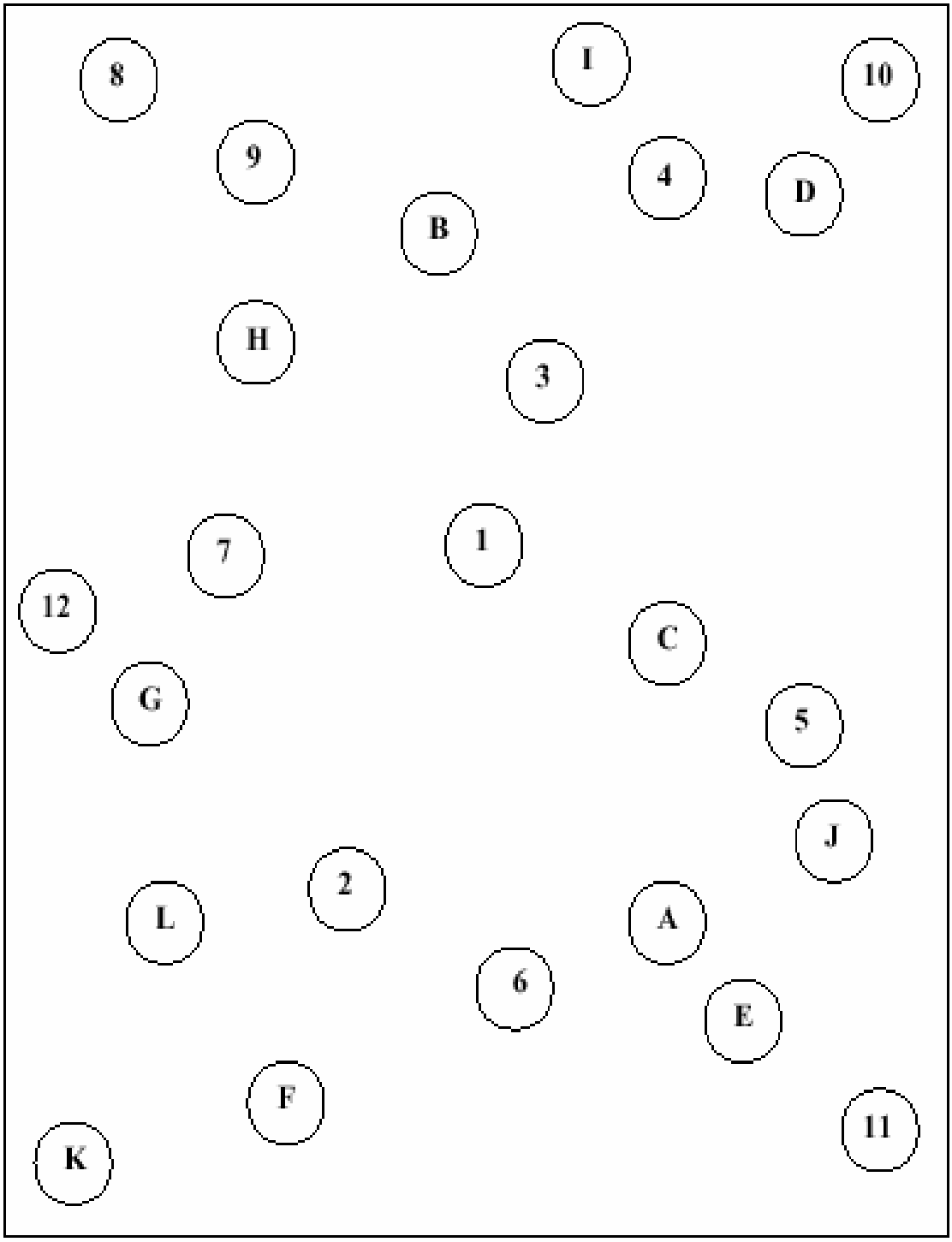
Patient's name: ..... Registration No:..... Date:.....



APPENDIX 7

Trail Marking Test B

TIME:



APPENDIX 8

STROOP COLOUR TEST SCORING

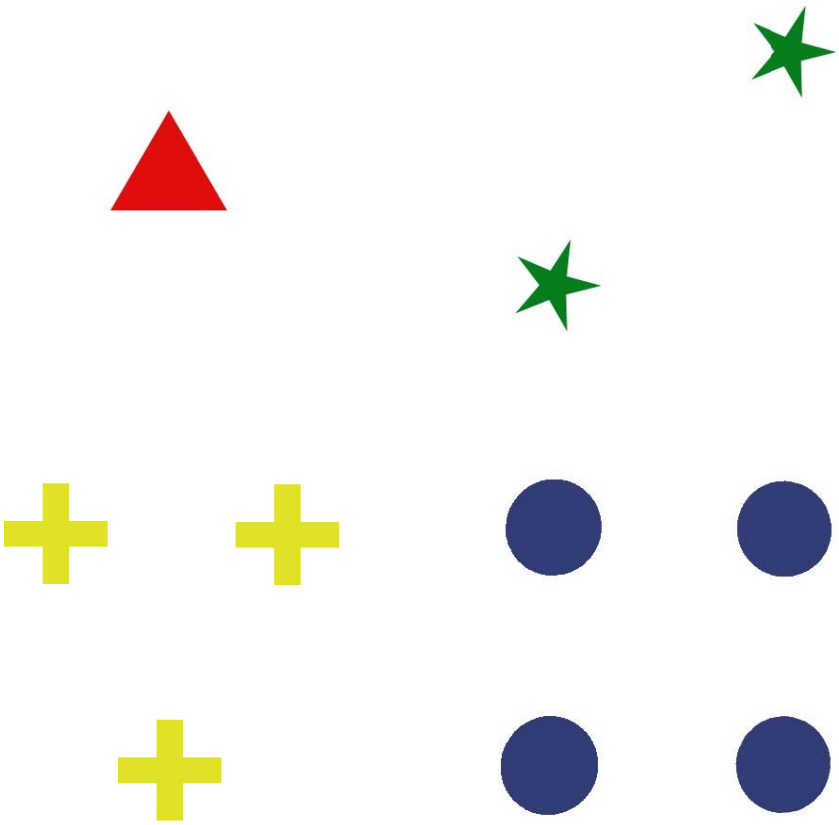
NAME:

CARD	NO. OF ERRORS	TIME TAKEN(t)
CARD I		
CARD II		
CARD III		

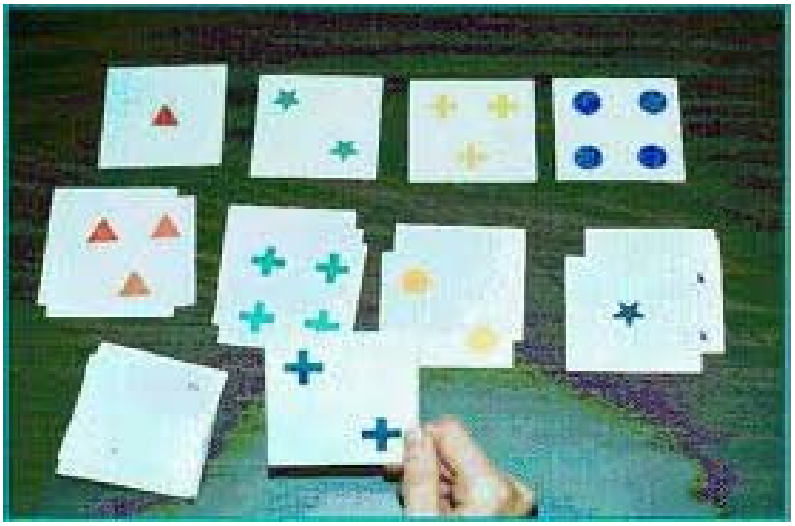
Stroop effect = t III – (t I + t II / 2)

APPENDIX 9

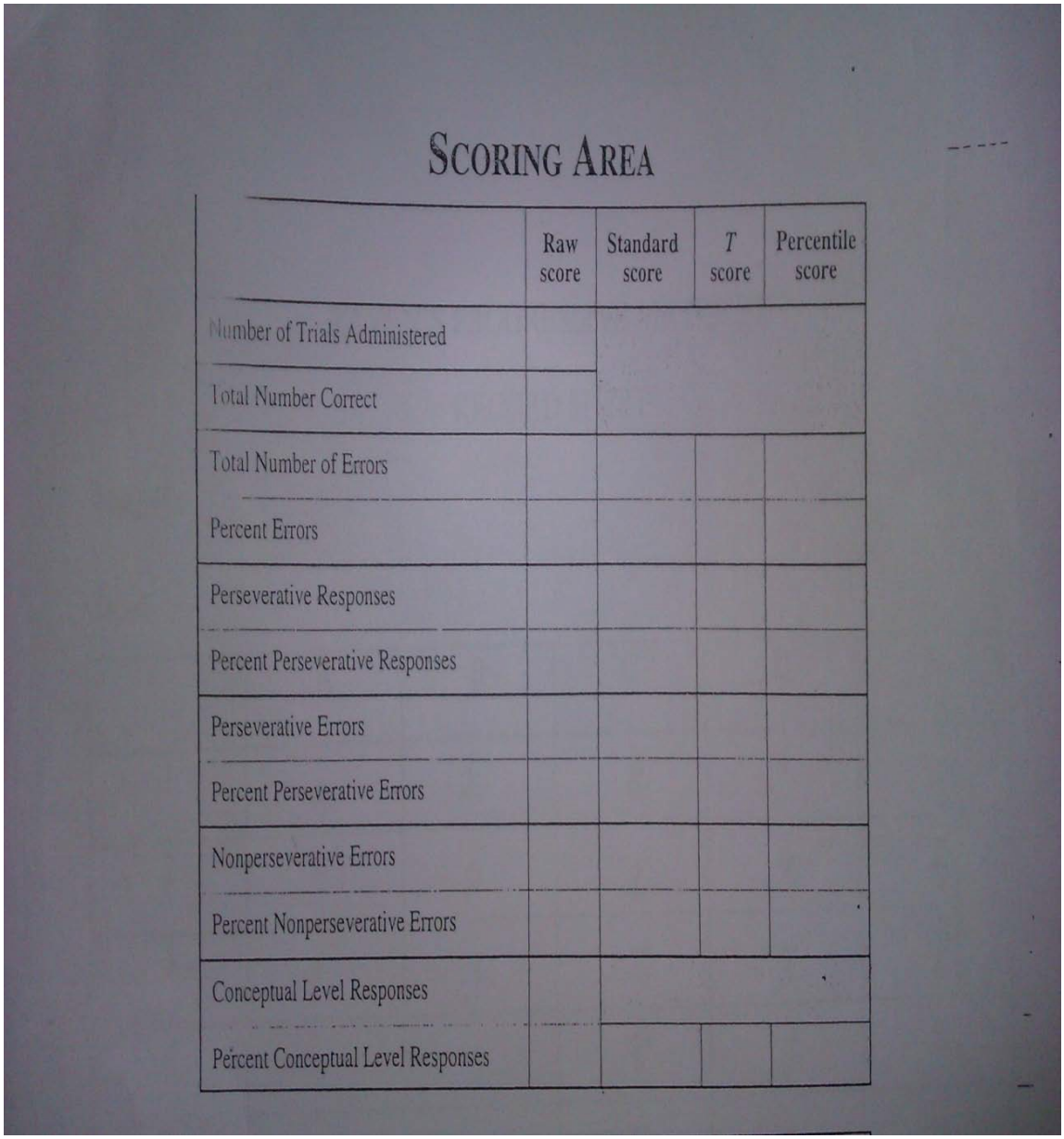
WISCONSIN CARD SORTING TEST STIMULUS CARDS



CARD SORTING



WCST SCORING SHEET



SCORING AREA

	Raw score	Standard score	*T* score	Percentile score
Number of Trials Administered				
Total Number Correct				
Total Number of Errors				
Percent Errors				
Perseverative Responses				
Percent Perseverative Responses				
Perseverative Errors				
Percent Perseverative Errors				
Nonperseverative Errors				
Percent Nonperseverative Errors				
Conceptual Level Responses				
Percent Conceptual Level Responses				